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(71) Applicant: Hagiwara, Yoshihide Takarazuka-shi Hyogo-ken (JP)

(72) Inventors:

Hagiwara, Hideaki
 Takarazuka-shi, Hyogo-ken (JP)

Aotsuka, Yasuyuki
 Koube-shi, Hyogo-ken (JP)

(74) Representative: Weisert, Annekäte, Dipl.-Ing. Dr.Ing. et al
Patentanwälte
Kraus Weisert & Partner
Thomas-Wimmer-Ring 15
D-80539 München (DE)

- (54) Amino acid sequences of anti-idiotypic antibodies against anti-cancer human monoclonal antibody, and dna base sequences encoding those sequences
- (57) Amino acid sequences of the H chain and L chain variable regions of mouse monoclonal antibodies Idio 3, Idio 17, Idio 20, Idio 27 and Idio 33 against idiotypes of a cancer cell antigen-specific human immunoglobulin CLN/IgG produced by a human/human fused cell strain CLN/SUZ H11, and base sequences of the genes of the variable regions are disclosed.

The above amino acid sequences and the base sequences are useful in medical and pharmaceutical fields such as prophylaxis, treatment and/or diagnosis of human diseases, and/or in pharmacological and/or biochemical fields, etc. such as biochemical reagents, and reagents for purification of biomacromolecules.

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### Description :

# Detailed Description of the Invention

ALIThis invention relates to the structure of the variable regions of mouse immunoglobulins against idiotypes of an antigen-specific human immunoglobulin, useful in wide fields, for example in pharmaceutical fields such as prophylaxis, treatment and/or diagnosis of human diseases, and/or in pharmacological and/or biochemical fields such as biochemical reagents and reagents for purification of biomacromolecules.

More detailedly, this invention relates to the amino acid sequences of the Hichain and Lichain variable regions of mouse immunoglobulins against idiotypes of a cancer cell antigen-specific human immunoglobulin produced by a human/human fused cell strain CLN/SUZ H11 from a B cell of a patient carrying human cervical carcinoma and a human lymphoblastoid cell strain, and relates to the base sequences of the genes of the variable regions.

Since the development of the technique of formation of monocional antibodies by cell fusion or immortalization of cells, many useful antibodies have been obtained using mainly mice. Among them, monoclonal antibodies against malignant tumor cells are utilized not only for fundamental researches such as analyses of tumor antigens, but in serum diagnoses, image diagnoses of tumors using labeled antibodies, and have extremely high utilization value. Particularly, human-derived anti-cancer monoclonal antibodies are expected as ideal antibodies in the clinical field, since they have only faint or no side effects.

In such circumstances, one of the present inventors, as disclosed detailedly in Japanese Laid-Open Patent Publication No. 201994/1983 (= U. S. Patent No. 5,286,647; EP-A-839,02157.3), Japanese Laid-Open Patent Publication No. 135898/1984 and Japanese Laid-Open Patent Publication No. 137497/1984, established a cell strain CLN/SUS H11 (ATCC No. HB 8307) which produces a human monoclonal antibody having a high reactivity with human cancer cells. Interesting findings are obtained about the antibody (named CLN-lgG) produced by this cell strain, that the antibody class is lgG; the isotypes are γ1 type and κ type; and the antibody binds to a cancer antigen immunohistologically existing on the surface of the cancer cells and moreover inhibits proliferation of the cancer cells. At present, the whole amino acid sequence and DNA base sequence of the antibody are clarified (Japanese Laid-Open Patent Publication No. 346792/1992 = WO 92/20799).

On the other hand, since Jerne put forward the so-called network theory, various researches have been made on the structure of the variable regions of antibodies. An antibody binds to an antigen at its variable region (antigen combining site). Therefore, the variable regions of antibodies have various three-dimensional-like structures in accordance with the structures of the antigenic determinants on the surfaces of antigens to be recognized. Thus, an antibody itself can be considered to be an antigen, and in the case, the structures of the variable regions of the antibody are called idiotypes, and antibodies against the idiotypes of the antibody are called anti-idiotypic antibodies. The structure corresponding to an antigenic determinant is called an idiotope. An idiotype can be thought to be an aggregate of idiotypes. It was reported that among anti-idiotypic antibodies (Ab2) against an antibody (Ab1) exist antibodies which competitively inhibit binding of Ab1 to an antigen and have idiotopes analogous to antigens recognized by the antibodies, i.e. antibodies having structures as so-called internal images of the antigen.

In view of the above findings, anti-idiotypic antibodies are expected to be utilized for the purpose of treatment and/or diagnosis of cancers.

For example, as for the purpose of cancer treatment, a vaccine therapy using an anti-idiotypic antibody as an antigen is made possible. It is generally difficult to get cancer antigens in large amounts, and it is restricted from a safety aspect and an ethical aspect to directly immunize human beings with cancer cells as antigens. Therefore, these problems can be avoided by performing immunization with an anti-idiotypic antibody in place of an antigen.

In a diagnostic aspect, anti-idiotypic antibodies can be utilized to examine the state of immune reactions against cancer cells. Specifically, it serves for early detection of cancers, judgment of therapeutic effects to detect or determine one's antibodies against cancer antigens existing in the blood or humor of cancer patients.

Under such technical background, problems as stated below are underlying to be solved.

1) When anti-idiotypic antibodies are utilized as vaccines or diagnostic drugs, it is necessary to provide these antibodies in large amounts and stably. 2) There is a possibility to give more powerful vaccines or diagnostic drugs abounding in functionality by altering or modifying the antibodies.

A method by gene manipulation is considered as a means for solving the above problems, i.e. a means for realizing improvement of production amount of the antibodies and elevation or modification of the activities of the antibodies.

For example, in the case of the problem of 1), it can be considered to solve the problem by cloning such an antibody gene, introducing the gene into host cells such as animal cells or <u>Escherichia coli</u>, expressing the antibody gene to give a large amount of the antibody, and in the case of the problem of 2), it can be considered to alter such an antibody so as to have stronger immunogenicity by artificially changing the antibody gene, or to design an antibody molecule having a higher vaccinal activity by adding a function which the antibody does not inherently have, for example an enzymatic activity, an immunity induction activity or the like to the antibody molecule or a fragment thereof.

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For accomplishment of these purposes, separation of anti-idiotypic antibody genes, and clarification of their struetures are necessary. However, there has not so far been known anything at all about the structures of L chains and H chains constituting anti-idiotypic antibodies against idiotypes of CLN-IgG, and the gene structures of the variable regions having a function to specifically bind to idiotopes of CLN-IgG.

Thus the main object of this invention is to clarify the gene structures of the L chains and the H chains of anti-CLNloG idiotype antibodies. La . 10. 3 . 5 . . .

. The present inventors have succeeded in creating hybridomas producing, respectively, five kinds of mouse anti-CLN-lqG idiotype antibodies (Idio 3, Idio 17, Idio 20, Idio 27 and Idio 33) having γ1 and icisotypes against the idiotypes of CLN-IgG; have separated, from the hybridomas, cDNAs encoding the L chains and H chains of the anti-idiotypic 10 antibodies, respectively; have clarified their DNA base sequences; have determined, based on these sequences; the amino acid sequences of the L chains and H chains of the antibodies; respectively; and have completed this invention.

Thus, according to this invention are provided an immunoglobulin H chain variable region fragment which contains a hypervariable region CDR1; having an amino acid sequence selected from a membra of a last content of the cont

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(3) Glu Glu Tyr Asp Tyr Asp Thr Leu Asp Tyr; Asp Arg Gly Gly Arg Asp Trp Tyr Phe Asp Val: Asp Gly Phe Leu Arg Asp Trp Tyr Phe Asp Val; and Ser Gly Tyr Tyr Gly Ser Phe Val Gly Phe Ala Tyr;

and DNA and RNA fragments encoding the immunoglobulin H chain variable region fragment.

According to this invention are further provided an immunoglobulin L chain fragment which contains a hypervariable region CDR1 having an amino acid sequence selected from

(1) Tyr Arg Ala Ser Lys Ser Val Ministration of the state of th Gln Leu His Leu Ala Ile Val Tyr Met His: Tyr Arg "Ala Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser Tyr Met His; San Decided to the San Decided to or walke green have been be Lys Ala Ser Gln Asp Val Asn CONTRACTOR SERVICES Thr Ala Val Ala; and A GARAN CONTRACT Lys Ala Ser Gln Asp Val Thr Thr Asp Val Ala,

40 a hypervariable region CDR2 having an amino acid sequence selected from 

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(2) Leu Val Ser Asn Leu Glu Ser;

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and a hypervariable region CDR3 having an amino acid sequence selected from

(3) Gln His Ile Arg Val Ala Tyr
Thr;
Gln His Ile Arg Gly Ala Tyr
Thr;
Gln His Ile Glu Gly Ala Tyr
Thr:
Gln Gln His Tyr Ser Pro Pro
Leu Thr; and
Gln Gln His Tyr Ser Thr Ala
Trp Thr;

and DNA and RNA fragments encoding the immunoglobulin L chain variable region fragment.

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In this invention, cytoplasmic RNAs were prepared from the five mouse hybridomas, respectively; the RNAs were converted to cDNAs by a reverse transcriptase; the antibody genes were amplified using these cDNAs as templates and using the PCR method; the amplified DNA fragments were integrated into plasmids and cloned; the base sequences of the insertion DNAs of the plasmids purified from <u>Escherichia coli</u> clones isolated were determined, and the amino acid sequences were determined based on the base sequences. These steps are further detailedly described below.

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# [1] Isolation of cytoplasmic RNAs

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Each mouse hybridoma is cultured and proliferated in a culture medium, e.g. and RDF or RPMI 1640 medium, containing 5% fetal bovine serum under a suitable condition, e.g. under a condition of 37°C and a carbon dioxide concentration of 5%; the resultant cells are collected by centrifugation; and the cytoplasmic RNA is extracted from the cells by a conventional method, e.g. a method disclosed in 7.12 of Molecular Cloning (2nd edition, edited by Sambrook et al., Cold Spring Harbor Laboratory Press 1989). The resultant cytoplasmic RNA can further be utilized as a template for cDNA synthesis. Specifically in this invention, the cytoplasmic RNAs were extracted from mouse hybridomas No. 3, No. 17, No. 20, No. 27 and No. 33, and previded for synthesis of cDNAs.

### [2] Synthesis of cDNAs

Using a cytoplasmic RNA obtained in the step of [1] as a template, a single-strand DNA complementary to the mRNA is synthesized in the presence of dATP, dGTP, dTTP and dCTP using, as a primer, an oligo dT corresponding to a poly A, or a synthetic nucleotide having a random sequence, and a reverse transcriptase. In the specific operations in the invention, cDNAs were synthesized using the cytoplasmic RNAs obtained in the step of [1] as templates and a random hexamer as a primer, respectively, and provided for the step of amplification of the antibody genes.

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### [3] Amplification of antibody genes by PCR

PCR reaction is performed in the presence of dATP, dGTP, dCTP and Taq polymerase using as a template a single-strand cDNA obtained in the step of [2] and as a primer a sequence of the antibody gene (e.g., a sequence encoding a constant region, a variable region or a leader region of the antibody gene) to amplify the antibody gene. Suitably in the invention, the antibody genes were amplified using as templates the single-strand cDNAs obtained in the step of [2] and using synthetic DNA oligomers corresponding to the sequences of the leader regions and variable regions of the L chains and H chains of the antibodies, respectively.

### [4] Cloning of PCR-amplified DNA fragments

A PCR-amplified DNA fragment obtained in the step of [3] is, directly or after treatment with restriction enzyme(s), ligated into one of various vectors, for example plasmid vectors such as pUC 18, pCR1000 and pCR<sup>TM</sup>, phage vectors such as M 13 phage, and phagemid vectors such as pUC 118 and pBluescrpt SK\* to prepare a vector containing the insertion fragment. Then, <u>Escherichia coli</u> is transformed with the vector, and a colony of the <u>Escherichia coli</u> containing

the targeted antibody gene fragment is obtained. The purified vector recovered from the <u>Escherichia coli</u> is provided as a sample for determination of the DNA base sequenc. In the specific operations in the invention, the PCR-amplified DNA fragments obtained in the step of [3] were directly ligated, respectively, into pCR1000 and pCR<sup>™</sup> plasmid vector; an <u>Escherichia coli</u> INVαF was transformed with each of the resultant plasmids; and the plasmids were purified from the resultant <u>Escherichia coli</u> colonies, respectively.

### [5] Determination of the base sequences and amino acid sequences of the DNAs

The base sequence of the DNA at the insection site in a plasmid obtained in the step of [4] can be determined using the Maxam-Gilbert method or the Sanger method. In the invention, the pCR1000 or pCR™ plasmid vectors containing the insection fragments were purified, respectively; their base sequences were determined by the Sanger method; and the amino acid sequences were presumed based on their base sequences, respectively.

Hereafter, this invention is further specifically described below according to examples.

Drawings referred to in Examples are briefly described as follows.

Fig. 1 is a drawing showing isotypes of monoclonal antibodies Idio 3, Idio 17, Idio 20, Idio 27 and Idio 33.

Fig. 2 is a drawing showing the monoclonal antibodies Idio 3, Idio 20, Idio 27 and Idio 33 specifically bind to CLIN-IgG, and do not bind to other human IgGs.

Fig. 3 is a drawing showing that monoclonal antibodies killo 3, killo 17, killo 20, killo 27 and killo 33 are competitively inhibiting the binding between CEN-IgG and human matrical carcinoma call ME-180.

20 Significations of monoclonal antibodies Idio 3, Idio 17, Idio 20, Idio 27 and Idio 33 are notated in parallel according to the Kabat's notation, and the regions of the Hypervariable regions CDR1, CDR2 and CDR3 are determined.

Fig. 5 is a drawing where the amino acid sequences of the L chain variable regions of monoclonal antibodies Idio 3, Idio 17, Idio 20, Idio 27 and Idio 33 are notated in parallel according to the Kabar's notation, and the regions of the hypervariable regions CDR1, CDR2 and CDR3 are determined.

## Example 1: Preparation of mouse hybridomas

100 μl of h mg/hil human lgG (produced by Cappel) is imraperitoneally injected to a Baib/c mouse on the first day after its birth to prepare a mouse having immuniclogical tolerance to human lgG. Six weeks later, the mouse is immunized as follows with CLN-lgG as an antigen:

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CLN-IgG purified from a culture medium of a human/human hybridoma CLN/SUZ H11 (ATCC No. HB8307) according to an ammonium sulfate precipitation method and protein A-affinity chromatography was adjusted to a concentration of 2 µg/µl with physiological saline; an equal amount of complete Freund's adjuvant solution was added; and after mixing and emulsification, 100 µl of the emulsion (corresponding to 100 µg of CLN-IgG) was subcutaneously injected into the immunologically tolerated mouse. Thereafter, similar immunization was repeated 4 to 5 times, the murine spleen was enucleated 4 days after the final immunization and made to be spleen cells, and they were used for the following cell fusion.

A mouse parent cells NS-1 (ATCC TIB-18) and the spleen cells are washed with portions of RPMI 1640 medium not containing serum, respectively, and the both of the cells are mixed and centrifuged. I ml of 50% polyethylene glycol (average molecular weight: 4,000) is added dropwise to the resultant precipitate over a period of 1 minute. 10 ml of RPMI 1640 medium is further added over a period of 3 minutes, the mixture is centrifuged at 400 x g for 5 minutes, the precipitate is suspended in 10 ml of RPMI 1640 medium containing 20% fetal bovine serum, and the suspension is spread into a 96-well microplate.

Thereafter, the cells were cultured in HAT medium for 14 to 21 days, transferred to HT medium, and finally cultured in HPWI 1640 medium containing 10% fetal bovine serum.

The articody titers in the curiure supernatants on the wells where proliferation was observed were assayed by an enzyme-labeled antibody technique; hybridoma clones secreting monoclonal antibodies which bind to CLN-IgG but not to human IgG were obtained from the appropriate wells by the limiting dilution method; and these hybridoma clones were named No. 5, No. 17, No. 20, No. 27 and No. 33.

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# Example 2: Determination of isotypes of the mouse antibodies

Isotypes of the antibodies secreted from the 5 mouse hybridomas obtained in Example 1 were determined as follows using a mouse monoclonal antibody isotyping kit (produced by Amersham Co.).

The mouse hybridomas are started to be cultured at a concentration each of 5 x 104/ml in portions of RPMI 1640 medium containing 10% fetal bovine serum, respectively, and 5 days later the culture supernatants are obtained, on stick portions of the typing sticks are placed in test tubes, respectively; 3 ml portions of the culture supernatants 5-fold diluted with TBS-T (Tris-buffered saline (TBS, pH 7.6) containing 0.1% Tween 20) are added thereto respectively; and

the mixtures are incubated a room temperature for 15 minutes. The culture supernatants are discarded, 5 ml portions of TBS-T are added, and the typing sticks are washed at room temperature for 5 minutes. TBS-T was discarded, and the washing was repeated once more. 3 ml portions of a peroxidase-labeled anti-mouse antibody 500-fold diluted with TBS-T are added, and the mixtures are incubated at room temperature for 15 minutes. The typing sticks are washed twice in the same manner as above; 3 ml portions of an enzyme substrate solution (obtained by adding one drop of 30% aqueous hydrogen peroxide to 50 ml of a TBS solution of 4-chloro-1-naphtol) are added; the mixtures are subjected to reaction at room temperature for 15 minutes; and then the sticks are washed with distilled water. The isotypes of the mouse antibodies are determined based on the resultant signals, respectively.

As a result, as shown in Fig. 1, all the isotypes of these antibodies; were y1 and k:

Example 3: Examination of specificities of the anti-idiotypic antibodies

600- ,ps. 5" d . Seatt we end the areas use temperates It was examined according to a dot blot technique, using an ECL Western blotting detecting reagent (produced by Amersham Co.), that the mouse anti-CLN-IgG idiotype antibodies specifically bind to CLN-IgG. The process is stated Seider in the Flat had see that ಹಾತ್ರ್\*ೀರ್ ಕತ್ತಿತ್ತ ಮಂತ್ರ

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"CLN-IgG and human IgG1 (produced by Protogen Co.) were diluted with RBS to concentrations of 50 to 0,2 µl/ml, respectively. 2 µl portions of the thus prepared samples were spotted on a number of Hybond-ECL nitrocellulose membrane (produced by Amersham,Co.), respectively and after being dried, the nitrocellulose membranes were allowed to stand at room temperature for one hour in PBS-T (0.3% Tween-20-containing PBS), containing 5% skim milk. After being washed with P.B.S.T, the nitrocellulose membranes were allowed to stand at room temperature for one hour in the culture supernatants (500-fold diluted with PBS-T) of mouse hybridemas No. 3, No. 17, No. 29, No. 27 and No. 33, respectively. After being washed with PBS-T, the nitrocellulose membranes were allowed to stand at room temperature for one hour in portions of a peroxidase-labeled sheep anti-mouse Igantibody 3,000-fold diluted with PBS-T, respectively. After being washed with PBS-T, the nitrocellulose membranes were subjected to reaction for one minute in portions of the ECL detecting reagent, and sheets of X-ray film were exposed for 30 seconds to the light emitted from the resultant nitrocellulose membranes, respectively.

The results of the sheets of X-ray film developed are shown in Fig. 2. Any, of the five antibodies bound to CLN-IgG, but did not bind to human IgG1. Namely, it was revealed that these antibodies are specific to CLN-IgG.

Next, it was examined whether or not the mouse antibodies have an activity to inhibit the binding of a human monoclonal antibody CLN-lgG to a human cancer cell. The method is stated below.

A human cervical carcinoma cell ME-180 (available from ATCC) is cultured in DF medium (a 1:1 mixed medium of DME: F-12) containing 10% fetal bovine serum. At the stage when the number of the cells becomes 5 x 106 to 1 x 107, the cells are detached from the bottom face of the Petri dish using trypsin, collected by centrifugation and sufficiently washed with the medium. A constant number (105/100 µl) each of the cells is placed in each well of a 96-well microtiter 35 plate, and allowed to stand at 37°C overnight to be attached on the plate. 50 µl portions of 3% glutaraldehyde solution were added dropwise into the respective wells, and the mixtures are allowed to stand at 37°C for 20 minutes to fix the cells. The cells of each well are centrifuged at 200 x g for 10 minutes and washed three times with a gelatin buffer (10 mM phosphate-buffered physiological saline containing 0.3% gelatin); 200 µl portions of 1% bovine serum albumin (BSA) solution are added dropwise; and the mixture is allowed to stand at 37°C for one hour to block the plate. The cells are washed three times with the gelatin buffer to remove BSA not adsorbed. Thereafter dilutions at various rates (100,to 1,000,000, fold) of the ascites obtained by intraperitoneally inoculating into mice the various hybridomas secreting the mouse anti-idiotypic antibodies are added dropwise together with CLN-IgG (50 µg each), and the mixtures are subjected to reaction at 37°C for one hour. The cells of these wells are washed three times with the gelatin buffer, 50 ul portions of a 3,000-fold diluted peroxidase-conjugated goat anti-human Ig antibody (produced by TACO Co.) are added dropwise, respectively, and the mixtures are subjected to reaction at 37°C for 30 minutes. The cells are washed three times with the gelatin buffer, and portions of a substrate solution containing hydrogen peroxide and o-phenylenediamine are edded to perform reaction in a darkroom. 10 minutes later, 50 µl portions of 5N sulfuric acid are added to stop the reaction. When the peroxidase-conjugated goat anti-Ig antibody remains on the microplate, namely when the human IgG to be bound thereto remains, a yellow reaction product having absorption at 490 nm is formed. The amount of CLN-IgG bound to the cancer cell is determined by measuring the amount of the reaction product by a spectrometer.

It was clarified, according to the above method, that all the mouse antibodies Idio 3, Idio 17, Idio 20, Idio 27 and Idio 33 inhibit the binding of CLN-IgG to the cancer cell (Fig. 3).  $_{6 - 500}$ 10 Buch

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From the foregoing, these mouse antibodies are antibodies against the idiotypes of CLN-IgG.

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## Example 4: Preparation of RNA

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Fr m the five kinds of mouse hybridomas No. 3, No. 17, No. 20, No. 27 and No. 33, the cytoplasmic RNAs were extracted according to the method disclosed in Molecular Cloning (2nd edition, edited by Sambrook et al., Cold Spring Harbor Laboratory Press 1989) 7, 12, as stated below. 17 M. 188. P

108 each of the hybridomas cells are collected by centrifugation, and washed twice with 10 times each precipitate's evolume of a phosphate-buffered saline. The cells of these groups are centrifuged at 2,000 x g and 4°C for 5 minutes, and the resultant precipitates are suspended in 200 µl portions of an RNA extracting solution (0.14 M NaCt, 1.5 mM MgCl<sub>2</sub>, 10 mM Tris-HCl pH 8.6, 0.5% Nonidet P-40, 1 mM dithiothreitol, 20 mM vanadylribonucleoside complex), respectively. The suspensions are subjected to vortex for 15 seconds and allowed to stand on ice for 5 minutes. The resultant suspensions are centrifuged at 12,000 x g for 30 seconds to remove the cell nuclei as precipitates; to the supernatants are, respectively, added 200 µl portions of a proteinase buffer (0.2 M Tris-HCl pH 8.0, 25 mM EDTA pH 8.0, 0.3 M NaCl, ்1.2% SDS) and 1 µl portions of an aqueous proteinase K solution (20 mg/ml); and the mixtures are sufficiently stirred and subjected to incubation at 37°C for 30 minutes. Equal volume portions of phenol/chloroform are added to the reaction 10 solutions, respectively, and the mixtures are stirred, centrifuged at 5,000 x g and room temperature for 10 minutes, and then allowed to separate into organic layers and aqueous layers, respectively, 400 µl portions of isopropanol cooled on gice in advance are added to the aqueous layers recovered, respectively, and the mixtures are allowed to stand on ice for 30 minutes. The mixtures are centrifuged at 12,000 x g and 4°C for 10 minutes to collect RNAs. The resultant RNA precipitates are washed with 1 ml portions of ethanol, dried under reduced pressure and suspended in appropriate 15 amount portions of TE buffer, respectively. Using the cytoplasmic RNAs obtained according to the above operations. the antibody genes are amplified. 

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## Example 5: Amplification and cloning of the antibody genes by the RT-PCR-method 1978 1978 1978

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20 The antibody genes were amplified from the cytoplasmic RNAs obtained in Example 4, using a GeneAmp® RNA PCR kit (produced by Takara Shuzo Co., Ltd.). First, 20 µl each of reactive solutions were prepared containing PCR buffer II (x1), 5 mM MgCl<sub>2</sub>, 1 mM dATP, 1 mM dGTP, 1 mM dTTP and 1 mM dCTP, 1 U/µl an RNase inhibitor, 2.5 µM a random hexamer, 2.5 U/µl a reverse transcriptase and 100 ng each of the above-mentioned cytoplasinic RNAs, respectively; 20 µl portions of a mineral oil were overlaid thereon respectively; and incubations were performed at room temperature for 10 minutes, at 42°C for 15 minutes, at 99°C for 5 minutes and then at 4°C for 5 minutes to perform cDNA synthesis by reverse transcription reaction. Then, 80 µl portions of a solution consisting of 4 µl of 25 mM MgCl<sub>2</sub>, 8 µl of 10½ PCR buffer II, 65.5 μl of sterile distilled water, 0.5 μl of AmpliTaq DNA polymerase (5 Ú/μl) and 2 μl of PCR primers "(each 100 pmoles) were added to the above 20 μl of the reverse transcription reaction solutions; 80 μl portions of the mineral oil were overlaid thereon; and PCR reactions were succeedingly performed. Each reaction was performed by 30 repeating 30 times the cycle of 94°C for 1.5 minutes, 50°C for 2 minutes and then 72°C for 3 minutes. The base sequences of the PCR primers are shown below. The primers contained in a lg-Prime™ kit (produced by Novagen Co.) were used Fexcept for the primer of the leader sequence C for H chains. The Medic Area is Belleville 1 if the Leader sequence is the chains. ত্ত্বিক্তি ক্ৰিক্সালে জানুষ্টি জন্মতিক্ৰিক্সা সময় সমূহ কৰি

and the second second	Primer for H chains	AND CONTRACTOR AND A STREET OF THE PROPERTY AS A STREE
mus Markeys to	Leader sequence A	5 GGGAATTCATGRASTTSKGGYTMARCTKGRTTT-3' +
erandi karangan dan dan dan dan dan dan dan dan dan d	Leader sequence B Leader sequence C	5 GGGAATTCÁTGRÁATGSASCTGGGTYWTYCTCTT 3 ST.
	Constant region	5' CCCAAGCTTCCAGGGRCCARKGGATARACIGRTGG 3'

The che deviations the longitud attack the control of

and the tree water to	Primer for L chains Leader sequence A   5: GGGAATTGATGRAGWGACAKWCYCAGGTCTTE 3'
******	
, the specification of the second control of	Leader sequence B 5' GGGAATTCATGGAGACACACACTCCTGCTAT 3'
For Star Const	Constant region 5' CCCAAGCTTACTGGATGGTGGGAAGATGGA 3'
STICL OF BUREAU	The substitute is previously sorted to the substitute of the larger than the

In the above, the alphabets other than A, G, C and T mean the following bases. R=A/G, W=A/T, I=inosine, Y=C/T, DEARCH, KEG/T, HEARCH, SEC/G, VEARCHG, MEARC, BEG/C/T

and output to the transfer the transfer of the total and the transfer of the t

10 μl portions of the resultant 100 μl each of the PCR reaction products are subjected to 1.5% agarose get electrophoresis, and it was confirmed that the antibody gene fragments each about 600 bp long were amplified. As a result, in the case of the H chains, the artibody genes derived from No. 3 and No. 17 were amplified in the leader sequence A

the antibody genes derived from No. 20 and No. 27 were amplified in the leader sequence B, and the antibody gene derived from No. 33 was amplified in the leader sequence C. On the other hand, in the L chains, the antibody genes derived from No. 27 and No. 33 were amplified in the case where the leader sequence A was used, and the antibody genes derived from No. 3, No. 17 and No. 20 were amplified in the leader sequence B.

Each of the RCR-amplified fragments about 600 bp long was integrated into pCR 1000 vector or pCR™ vector using TA cloning kit (produced by Invitogen Co.). Specifically, ligation mix solutions were prepared by mixing 1 µl portions of the PCR reaction products, 1:µl portions of 10 x the ligation buffer, 2 µl portions of pCR1000 or pCRM vector (corresponding to 50 µg), 1 µl of T4 DNA ligase and 6 µl portions of sterilized water, respectively; and incubated overnight at 12°C. Separately, 50 μl portions of a suspension of a competent Escherichia coli INVαT strain, to which portions were 10 added 2 μl portions of 0.5 Mβ-mercaptoethanol, respectively, were prepared; and 1 μl portions of the above ligation mix solutions are added thereto, respectively. The mixtures are allowed to stand on ice for 30 minutes, incubated at 42°C for one-minute, and rapidly cooled on ice for 2 minutes. 450 µl portions of SOC medium warmed to 42°C in advance were added to the resultant Escherichia coli solutions, respectively, and the mixtures are cultured with shaking at 37°C for one hour. Measwhile, 25 µl portions of X-Gal (40 mg/µl) are spreaded onto a number of LB agarplates each containing Kanamycin (50 µg/ml), respectively, and the agar plates are incubated at 37°C until each X-Gal completely permeates words a serie disable of the agar plate.

200 ut portions of the Escherichia coli culture broths after completion of culture were spread on the agar plate dried, respectively, and the plates were allowed to stand at 37°C overnight to give white colonies each having Kanamycin

Plasmids were purified from the Escherichia coli clones containing the respective entibody genes, and named 😘 3KB11, 17KB1, 20KB1, 27KA2, 33KA26, 3GB1, 17GB7, 20GA2, 27GA5 and 33GC003, respectively. Purification of the  $s^{\Gamma}$ K + 1 Sec in plasmids is performed as follows. the second second , . . #

The Escherichia coli strains containing the above plasmids, respectively, are cultured 37°C overnight in 100 ml portions of LB medium containing Kanamycin (50 µg/ml), respectively. Each of the resultant culture broths is centrifuged 25 / at 3,000 rpm for 10 minutes; the cells collected are suspended in 3 ml of an ice-cooled suspension (50 mM glucose; 10 mM EDTA, 2 mM Tris-HCl pH 8.0); and the suspension is allowed to stand at room temperature for 5 minutes. 6 ml of an alkali lysing solution (0.2 N sodium hydroxide, 1% SDS) is added, and the mixture is mixed by gently turning the centrifugation vassel upside down, and allowed to stand on ice for 5 minutes. 4.5 ml of an ice-cooled neutralizing solution (5 M potassium acetate pH 4.8) is added, and the mixture is centrifuged at 12,000 rpm and 4°C for 10 minutes. The supernatant is transferred into another centrifugation vessel; 1 ml of heat-treated 100 µg/ml RNase A solution is added; and the mixture is subjected to reaction for one hour in an incubator of 37°C to perform RNA digestion. To the reaction solution are added 6 ml of TE buffer-saturated phenol and 6 ml of chloroform/isoamyl alcohol (24:1), and the mixture is subjected to vortex for 30 seconds and then centrifuged at 10,000 rpm and 4°C for 3 minutes. The aqueous layer is transferred into another centrifugation vessel, an equal amount of isopropanol is added, and the mixture is sufficiently mixed and then centrifuged at 10,000 rpm and room temperature for 10 minutes.

The resultant precipitate is washed with 1 ml of 70% cold (-20°C) ethanol, dried under reduced pressure, and dissolved in 480:ul of sterilized water. The solution is transferred into an Eppendorf tube; 120 µl of 4 M NaCl and 600 µl of 13% polyethylene glycol #6900 are added; and the mixture is allowed to stand on ice for 20 minutes. The mixture is then centrifuged at 10,000 rpm and 4°C for 10 minutes, and the precipitate is washed with 1 ml of 70% cold (-20°C) ethanol, dried under reduced pressure and dissolved in 100 µl of TE buffer. The resultant purified plasmid was used as a templat THE CONTROL WASHINGTON CONTROL for sequencing reaction.

### Example 6: Determination of the base sequences

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Sanger reactions were performed using as templates the plasmids cloning purified in Example 5 and a fluorescencelabeled primer; the reaction products were analyzed by a DNA sequencer DSQ-1 (produced by Shimadzu Corporation); and the DNA base sequences of the insert parts of the plasmids were also determined:

The sequencing reactions were performed using AmpliTaq cycle sequencing kit (produced by Takara Shuzo Co., Ltd.) and a fluorescence-labeled primer in a reagent kit (produced by Wakunaga Pharmaceutical Co., Ltd.) exclusively used for a fluorencene-type DNA sequencer. First, 2 to 4 µg of one of the plasmids purified as stated in Example 5 is mixed with 1 µl of the FITC-labeled primer (1 p mole/µl, forward or reverse is used) and 2 µl of the 10 x cycling mix solution, and sterilized water is added to prepare 10 µl in final volume of a reaction mix! Four tubes are prepared in which 2 µl portions of the termination mix (A, G, C, T) were placed in advance, respectively. 2 µl portions of the above reaction mix were taken and placed into the respective tubes. The mixtures are corrected by centrifugation, 10 µl portions of a mineral oil ar overlaid, and cycling reactions are performed under the following conditions; Precycle 95°C, 3 minutes; first cycle 95°C 30 seconds, 60°C 30 seconds, 72°C 1 minute (repeated 15 times); second cycle 95°C 30 seconds, 72°C 1, minute (repeated 15 times); postcycle 4°C. المحج مرولا ١٩٠١ سا

2 μl portions of a reaction-stopping dye solution (95% formaldehyde, 20 mM EDTA, 0.05% methyl violet) are added, and the mixtures are mixed by centrifugation and preserved at 20°C until they are electrophoresed.

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As 5% polyacrylamide gel was used one obtained by adding pur water to 30 g of tirea, 6 mi of 10 x TBE buffer (0.89 M Tris-HCl, 0.89 M boric acid, 0.025 M EDTA disodium salt) and 10 ml of 30% acrylamide solution (28.5% acrylamide and 1.5% methylenebisacrylamide, both produced by BIO-RAD Co.) to make the whole volume 60 ml; filtering the mixture with 0.22- $\mu$ m filter; deaerating the filtrate for 30 minutes; adding 150  $\mu$ l of 10% ammonium persulfate and 15  $\mu$ l of TEMEO; allowing the mixture to stand overnight to make it gel.

The gel was set in the DNA sequencer DSQ-1, and prerun was performed at a constant voltage of 1,000 V for one hour. Each of the samples was denatured at 95°C for 3 minutes immediately before electrophoresis, and rapidly cooled on ice, and 2 to 3  $\mu$ l of the reaction solution was sucked up from the bottom part of the tube by a micro-syringe and loaded onto the gel. Samples run was performed at a constant electric power of 20 W for 12 hours.

After completion of electrophoresis, the base sequence was determined using the software attached to DSO-1. The sequence was confirmed by sequencing both of the sense and antisense chains of the same plasmid from both directions.

The resultant base sequences of the variable regions of the H chains and L chains of the five kinds of the mouse monoclonal antibodies, and amino acid sequences presumed therefrom are shown in the following sequence listing. Relation between the sequence numbers and the sequences of the clones are as follows:

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Sequence No. 1 : Idio 3 H chain variable region (clone 3GB1)
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Sequence No. 2: Idio 17 H chain variable region (clone 1.7GB7)

Sequence No. 3: Idio 20 H chain variable region (clone 20GA2)

Sequence No. 4: Idio 27 H chain variable region (clone 27GA5)

Sequence No. 5: Idio 33 H chain variable region (clone 33GC003)

Sequence No. 6: Idio 3 L chain variable region (clone 3KB11)

Sequence No. 7: Idio 17 L chain variable region (clone 17KB1)

Sequence No. 8 : Idio 20 L chain variable region (clone 20KB1)

Sequence No. 9: Idio 27 L chain variable region (clone 27KA2)

Sequence No.10: Idio 33 L chain variable region (clone 33KA26)

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# Example 7 Determination of hypervariable regions

The amino acid sequences obtained in Example 6 were notated in parallel according to the numbering of Kabat et al.'s data base (Sequences of proteins of immunological interest Fifth edition, U. S. Department of health and human services. Public health service, National Institutes of Health. NIH Publication No. 91-3242, Kabat et al. 1991), and the amino acid sequences of the hypervariable regions CDR1, CDR2 and CDR3 of each antibody were identified (Fig. 4, H chains, Fig. 5 L chains). In order to confirm the novelty of the identified amino acid sequences of the hypervariable regions CDR1, CDR2 and CDR3, retrieval by a computer was performed using the above Kabat et al.'s data base and a protein data base NBRF-PDB (National Biomedical Research Foundation - protein data base) Release 36.

As a result, the amino acid sequences of Idio 3:H chain CDR1, Idio 17 H chain CDR1, Idio 20 H chain CDR1, Idio 27 H chain CDR1, Idio 33 H chain CDR2, Idio 3 L chain CDR2, Idio 17 L chain CDR2, Idio 27 L chain CDR2 and Idio 33 L chain CDR2 were the same as those of known antibodies, but the amino acid sequences of other CDRs were

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revealed to be novel seguences.

GCC AAA ACG ACA CCC

Ala Lys Thr Thr Pro

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Sequence Listing Seq. I.D. number : 1 Sequence length: 399 Sequence type : nucleic acid Strandedness : double 1300 3000 Topology : linear 10 Sequence kind : mRNAbeset to and Original source . : : 1 15 C with the report of the statements. n. : . Organism : mouse is one, in those we allowed 23 20 6 4 ou into 1 mem on and the sound of the control of κυ°<sub>ε</sub> 8 . 15 Sequence characteristics Symbol expressing characteristics : CDS ising the contract of accounted 17 10t 5 1 Se 1. 1. 1. Side cores, and Presence position: 1.,399 A fire with the the constant of the Characteristics determination method: S 3 3 3 823 20 Characteristics determination method @ Some number of the common of the ។ ស្នង នេះ បាននៃក 🚅 បានស៊ី 🗘 🤚 សែច ៤២៦ភ៍ S. 19 6 Sequence 25 CTG TCG GTA ACT TCA GGG GTC TAC TCA GAG GTT CAG CTC CAG CAG TCT 48 Leu Ser Val Thr Ser Gly Val Tyr Ser Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala Ser Val Lys Met Ser Cys Lys Stills on the Angliot of the control GCT TCG GGC TAC ACG TTT AAC AGC TAC TGG ATG CAC TGG GTA AAA CAG 144 With Road of Ala, Ser Gly Tyr Thr. Phe Ash Ser Tyr Trp Met His Trp Val Lys Gln (10) 70 1 m 1 27 安 95m - 新 25. 北 北 1、 1、 1、 14 14 30 \* 生態 水門 ( \* 1. 635 ) 。 s - á c a ff - a 1921674 35 ( D) 10 O THE AGG COCTEGGA CACHGGT CTG GAA TGG ATTEGGC GCG ATTETAT, CCCHEGGA AAT Charles Hill out the Till Argipro GIV Gin Gry Deu Gill Tro Tile Gly Als Tile Tyr Pro Gly Asn Light of mast but read the removation self at an energy 55 S Direited 1900 19 440 AGT GAT ATT AGC TAC AGC CAG AAC TIT AAG GAC AGG GCC AAA CTG ACT 240 Ser Asp Ile Ser Tyr Ser Gln Asn Phe Lys Asp Arg Ala Lys Leu Thr 60 GCC GTC ACA TCC ACC AGC ACT GCC TAC ATG GAA CTC AGA AGC CTG ACA 288 Ala Val Thr Ser Thr Ser Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr AAT GAG GAC TCT GCG GTC TAT TTC TGT ACA AAA GAG GAA TAT GAT TAC 336 45 Asn Glu Asp Ser Ala Val Tyr Phe Cys Thr Lys Glu Glu Tyr Asp Tyr 95 GAC ACC CTG GAC TAC TGG GGT CAA GGA ACC TCA GTC ACC GTC TCC TCA 384 Asp Thr Leu Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser 50 110 105

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Sequence Listing

5	Seq. I.D. number : 2
	Sequence length: 402
	Sequence type : nucleic acid
	Strandedness : double
10	Topology: linear
	Sequence kind: mRNA
	Original source
	Organism : mouse
15	Sequence characteristics
	Symbol expressing characteristics : CDS
	Presence position: 1402
•	Characteristics determination method: S
20	Symbol expressing characteristics : sig peptide
	Presence position : 130
	Characteristics determination method : S
	Sequence: the probability of the second of t
25	ATT CTG TOG STA ACT TOA GGG GTC TAC TOA GAG GTT CAG CTC CAG CAG
	Ile Leu Ser Val Thr Ser Gly Val Tyr Ser Glu Val Gln Leu Gln Gln
	-10
20	TCT GGG ACT GTG CTG GCA AGG CCT GGG GCT TCA GTG AAG ATG TCC TGC 96
3 <i>0</i> .	Ser Gly Thr Val Leu Ala Arg Pro Gly Ala Ser Val Lys Met Ser Cys
	AAG GCT TCG GGC TAC ACC TTT AAC AGC TAC TGG ATG CAC TGG GTA AAA
	Lys Ala Ser Gly Tyr Thr Phe Asn Ser Tyr Trp Met His Trp Val Lys
35	25 30 100 000 000 000 000 000 000 000 000 0
	CAG AGG CCT GGA CAG GGT CTG GAA TGG ATT GGC GCG ATT TAT CCT GGA 19 Gln Arg Pro Gly Gln Gly Len Glu Tro 11e Gly Ala 11e Tyr pro Gly
	40 state and a 1 45 feet to 190 garden 50 year ear garden
	AAT AGT GAT ATT AGC TAC AGC CAG AAC TIT ARG GAC AGG GCC AAA CTG : 24
40	Asn Ser Asp Ile Ser Tyr Ser Gln Asn Pha Lys Asp Arg Ala Lys Leu
	ACT GCC GTC ACA TCC ACC AGC ACT GCC TAC ATG GAA CTC AGA AGC CTG 28
	Thr Ala Val Thr Ser Tax Ser Thr Ala Tyx Met Glu Leu Arg Ser Leu f
	70 See 1980 1980 1980 1975 1970 1992 1970 1972 1973 1973 1970 1970 1970 1970 1970 1970 1970 1970
45	ACA AAT GAG GAC TCT GCG GTC TAT TTC TGT ACA AAA GAG GAA TAT GAT
	The Asn Glu Aspeser Ala Val Tyr Phe Cys Thr Lys Glu Glu Tyr Asp
	TAC GAC ACC CTG GAC TAC TGG GGT CAA GGA ACC TCA GTC ACC GTC TCC 384
	Tyr Asp Thr Leu Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
50	105 flor ten Ant An 110
	TCA GCC AAA ACG ACA CCC
	Ser Ala Lys Thr Thr Pro 120

	Sequence Listing	• •
	Seq. I.D. number : 3	
,	Sequence length: 438	= 3
	Sequence type : nucleic acid	1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1
	Strandedness : double	
	Topology : linear	: 27
	Sequence kind: mRNA	
	Original source	
	Organism : mouse	
	Sequence characteristics	
15	Symbol expressing characteristics : CDS	- "~ (4)
	Presence position: 1438	. 1 . 70
•		
	Characteristics determination method: S	4 1 - 4 20 16 16
20	Symbol expressing characteristics : sig peptide	12.12
• ,	Presence position: 15/	
•	Characteristics determination method: S	
	Sequence	
25	ATG GAG TTC GGG CTA AAC TGG GTT TTC CTT GTA ACA CTT TTA AAT	
	Met Glu Phe Gly Leu Asn Tro Val Phe Leu Val Thr Leu Leu Asn	
	ATC CAG TGT GAG GTG AAG CTG GTG GAG TCT GGA GGA GGC TTG GTA	
	Ile Gln Cys Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val	
30	10 mg	
	CCT GGG GGT TCT CTC AGA CTC TCC TGT GCA ACT TCT GGG TTA ACC	,
	Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Leu Thr	
	ACT GAT TAC TAC ATG AAC TGG GTC CGC CAG CCT CCA GGA AAG GAA	CTT 192
35	Thr Asp Tyr Tyr Met Asn Trp Val Arg Gln Pro Pro Gly Lys Glu	
<b>.</b>	30 - 30 - 35 - 35 - 35 - 35 - 36 - 36 - 36 - 36	eeri . 
	GAA TOG TTG GGT TTT ATT AGA AGC AAA GCT AAT CTT TAC ACA ACA	
	Glu Trp Leu Gly Phe Ile Arg Asn Lys Ala Asn Leu Tyr Thr Thr Thr 1	ASP 60
40	TAC AGT GCA TOT GTG ANG GGT CGG TTC ACC ATC TCC AGA GAT AAT	
40	Tyr Ser Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn	Pro
	188 ON THE ABS 650 AND LIA THE CLETO SECOND OF SECTION AND	1 . A
	CAA AGC ATC CEC TAT CET CAA ATG AAC ACC CTG ACADACT GAG GAC	
	Gln Ser Ile Leu Tyr Leu Gln Met Asn Thr Leu Thr Thr Glu Asp	
45	THE PART OF THE PA	
	GCC ACT TAT TAG TGT GCA AGA GAT AGG GGG GGG AGG GAC TGG CTAC !  Ala Thr Tyr Tyr Cys Ala Arg Asp Arg Gly Gly Arg Asp Trp Tyr !	
	95 4 100 <sub>(00)</sub> 4 100 <sub>(00)</sub> 105 <sub>(00)</sub> 105 <sub>(00)</sub>	
	GAT GTC TGG GGC GCA GGG ACC ACG GTC ACC GTC TCA GGC AAA	
50 ·	Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Lys	Thr
	110 115 120 120 120 120 120 120 120 120 120 120	1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2
	The Pro	5. 59 P
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Sequence Listing

5	Seq. I.D. number : 4	
	Sequence length: 411	., .
	Sequence type : nucleic acid	• •
	Strandedness: double	
••	Topology : linear	
10	Sequence kind: mRNA	
	Original source	
	Organism : mouse	
	Sequence characteristics	
15	Symbol expressing characteristics : CDS	· · · · · · · · · · · · · · · · · · ·
	Presence position: 1411	, , , , , ,
	Characteristics determination method: S	
20	Symbol expressing characteristics : sig peptide	
	Programs position + 1 20	•
	Characteristics determination method: S	
	Sequence	°
25 ·	CIT GTA ACA CGT TTA AAT GGT ATC CAG TGT GAG GTG AAG CTG GTG G	<u> </u>
	Led Val Thr Arg Leu Asn Gly Ile Gln Cys Glu Val Lys Leu Val Gl	MG 48.
	-10 -5 . 1	5
	TCT GGA GGA GGC TTG GTA CAG CCT GGG GGT TCT CTG AGA CTC TCC TC	T 96
30	Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser C	rs 🖟 💯
	GCA ACT TOT GGG TIC ACC TIC ACT GAT TAC TAC ATG AAC TGG GTC GG	**************************************
	Ala Thr Ser Gly Phe Thr Phe Thr Asp Tyr Tyr Met Asp Trp Val Ar	
	25 30	Transfer to a
35	CAG CCT CCA GGA AAG GCA CTT GAG TGG TTG GGT TTT ATT AGA AAC AA	A 192
	Gln Pro Pro Gly Lys Ala Leu Glu Tro Leu Gly Phe Tie Arg Asn Ly	Sin in the same
	GCT AAT TAT TAC ACA ACA GAG TAC AGT GCA TCT GTG AAG GGT CGG TT	
	Ala Asn Tyr Tyr Thr Glu Tyr Ser Ala Ser Val Lys Gly Arg Ph	କୁ: 1 ଅଫର ଅଟ
10	55 60 50 50 50 50 50 50 50 50 50 50 50 50 50	ନ୍ତି ଓଡ଼ିଆ ମଧ୍ୟ
	ACC ATC TCC AGA GAT AAT TCC CAA AGC ATC CTC TAT CIT CAA ATG AA Thr Ile Ser Arg Asp Asn Ser Gln Ser Ile Leu Tyr Leu Gln Met As	C 288
	70' 2 75' 75' 80' 80' 80' 80' 80' 80' 80' 80' 80' 80	
	ACC CTG AGA GET GAS GAC AGT GCC ACT TAT TAC TGT GCA AGA GAT GG	- G 336 🔼
15	Thr Leu Arg Ala Glu Asp Ser Ala Thr Tyr Tyr Cys Ala Arg Asp Gl	,
	TTC CTA CGG GAC TYS TAC TYC CAT CTC TYC CGG GAC AND	Taran Jan 16
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50	ACC CTC TCC TCA CCC ARA ACC ACC	*
	ACC GTC TCC TCA GCC AAA ACG ACA CCC	. 4417 - 24
	120 125	

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	Sequence Listing	
5	Seq. I.D. number : 5	
	Sequence length: 363	
	Sequence type : nucleic acid	
	Strandedness: double	
10	Topology: linear	,
•	Sequence kind: mRNA	•
	Original source	
15	Organism: mouse	
	Sequence characteristics	
	Symbol expressing characteristics : CDS	
20	Presence position: 1363	
20	Characteristics determination method: S	
	Sequence The second of the months of the takense	
	200 200 200 200 200 200 200 200 200 200	18
25	Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala	. •
	10 1.5	
		96
30	Ser Val Asn Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr	
		.44
	Trp Met Gln Trp Val Tys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile	
	35 TO THE WAR TO SEE OF ACCUSE OF ACCUSE ACCUSED ACCUS	
35	GGG GCT ATT TAT CCT GGA GAT GGT GAT ACT AGG TAC ACT CAG AAG TTC . 1	92
	Gly Ala Ile Tyr Pro Gly Asp Gly Asp Thr Arg Tyr Thr Gln Lys Phe	
	the control of the co	40
40	Lys Gly Lys Ala Thr Leu Thr Ala Ala Lys Ser Ser Ser Thr Ala Tyr	10
	65 70 70 Sept. 10 10 10 10 10 10 10 10 10 10 10 10 10	
	ATG CAA CTC AGC AGC TTG GCA TCT GAG GAC TCT GCG GTC TAT TAC TGT - 2	88
	Met Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Tyr Cys	
45	80	36
	GCA AGA TCG GGC TAC TAT GGT AGC TTC GTT GGG TTT GCT TAC TGG GGC 3  Ala Arg Ser Gly Tyr Tyr Gly Ser Phe Val Gly Phe Ala Tyr Trp Gly	36
	100 105 105 110	
50	CAA GGG ACT CTG GTC ACT GTC TCT GCA	63
٠	Gln Gly Thr Leu Val Thr Val Ser Ala-	
	115 120°13 (1,81) # 120°13 (1,81) # 120°13 (1,81)	

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Sequence Listing

5	Seq. I.D. number : 6	
	Sequence length: 354	
	Sequence type : nucleic acid	
	Strandedness : double	
10	Topology: linear	
	Sequence kind: mRNA	
	Original source	
15	Organism : mouse	
	Sequence characteristics	
	Symbol expressing characteristics: CDS	
••	Presence position :- 1354	
20	Characteristics determination method : S	
	Sequence The Sequence	•
	CAC ATTE CTC CTC ACA CAC MCT COTT COTT COTT COTT CTC	18
25	Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Pro Leu	
	1 5 10 15	
		96
30	Gly Gln Arg Ala Thr Ile Ser Tyr Arg Ala Ser Lys Ser Val Gln Leu 20 25 30	
		.44
	His Leu Ala Ile Val Tyr Met His Trp Asn Gln Gln Lys Pro Gly Gln	
	35 (a) (b) (c) (c) (c) (c) (c) (c) (c) (c) (c) (c	
35	CCA CCC AGA CTC CTC ATC TAT CTT GTA TCC AAC CTA GAA TCT GGG GTC  Pro Pro Arg Leu Leu Ile Tyr Leu Val Ser Asn Leu Glu Ser Gly Val	.92
	e s 50 d d data grand to 1955sen die AAR met dat Ger Gry Van	
	CCT GCC AGG TTC AGT GGC AGT GGG TCT GGG ACA GAC TIC ACC CTC AAC 2	40
<b>10</b>	Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn	
	70 75 75 75 75 75 75 75 75 75 75 75 75 75	
	Ile His Pro Val Glu Glu Asp Ala Ala The Tyr Tyr Cys Gln His:	88
	80 90 10 10 10 10 10 10 10 10 10 10 10 10 10	
15		36
	Ile Arg Val Ala Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu lle Lys	
	CCC CCT CAT CCT CCA	C A
50	Arg Ala Asp Ala Pro	54
	nc <b>1.15</b>	

		Sequence Disting	
5		Seq. I.D. number: 7	
•		Sequence length: 438	
		Sequence type : nucleic acid	
		Strandedness: double	
10		Topology: linear	
,,		Sequence kind: mRNA : % Joqui	
		Original source	
		Organism : mouse characterism to	
15		Sequence characteristics	
		Symbol expressing characteristics : CDS	
		Presence position: 1438	
·		Characteristics determination method : S	
20		Symbol expressing characteristics : sig peptide 50 2835	
		Presence positions: 139 to the same to de the same a rate.	
	•	Characteristics determination method : S	
		Sequence	
25	1	CTA TGG GTA CTG CTC TGG GTT CCA GGT TCC ACT GGT GAC ATT GTG. 48	
		Leu Trp Val Leu Leu Trp Val Pro Gly Ser Thr Gly Asp Ile Val	
		-10 -5.	
	3.5	CTG ACA CAG TCT CCT GCT TCC TTA GCT GTA TCT CTG GGG CAG AGG GCC 96	
30		Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Ala Ser Leu Blo 15	
		TOO ATO TOA TAC AGG GCC AGC AAA AGT GTC AGT ACA TOT GGC TAT AGT	
	•	Ser Ile Ser Tyr Arg Ala Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser	
		20 25 30	
35	:	TAT ATG CAC TGG AAC CAA CAG AAA CCA GGA CAG CCA CCC AGA CTC CTC 192  Tyr Met his Trp Asn Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu	
-		35% po 10. 12. 140 size 200 sono 25 45 10 613 120 20 20 50 10 020	
		ATC TAT CTT GTA TCC AAC CTA GAA TCT GGG GTC CCT GCC AGG TTC AGT 240	
	. 1	Ile Tyr Leu Val Ser Asn Leu Glu Ser Gly Val Pro Ala ArgsPhe Ser	
40		GGC AGT GGG TCT GGG ACA GAC TTC ACC CTC AAC ATC CAT CCT GTG GAG 288	
		Olse Com Olse Con Olse Mars Age Who Mars Lou Bon The side was seed of	
		Gly Ser Gly Sel Gly Int ASP Pile Int Let ASI The His Pro Val Gly	
		GAG GAG GAT GCT GCA ACC TAT TAC TGT CAG CAC ATT AGG GGA GCT TAC 336	
45		Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ile Arg Gly Ala Tyr	
		N85 A CO GGG GGG ACC AAG CTG GAA ATA AAA CGG GCE GAT/GCT GCA 384	
		Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala	
		100 105 110	
50	-	CCA ACT GTA TCC ATC TTC CCA CCA TCC AGT AAG CTT GGG AAA CGG TTC 432	
		Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Lys Leu Gly Lys Arg Phe	
		115 120 125 130	
		GCA CCG 438 Ala Pro	
		-	

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# EF 0,702:082 A1

Sequence Listing

5	Seq. I.D. number: 8	
9	Sequence length: 417	
	Sequence type : nucleic acid	
	Strandedness: double	
10	Topology : linear	
	Sequence kind: mRNA	
	Original source	•
	Organism : mouse	
15	Sequence characteristics	
	Symbol expressing characteristics : CDS	
	Presence position: 28417	
	Characteristics determination method: S	
20	Symbol expressing characteristics as signeptide	
	Presence position: 2890	
•	Characteristics determination method : S	
25	Sequence  GGCCGCG GTGAGAACCG TTGGGAATTC ATG GAG ACA GAC ACA CTC CTG	48
	Met Glu Thr Asp Thr Leu Leu	48
	-20 -15	
	CTA TGG GTA CTG CTG CTC TGG GTT CCA GGT TCC ACT GGT GAC ATT GTG	
30	Leu Trp Val Leu Leu Leu Trp Val Pro Gly Ser Thr Gly Asp Ile Val	·'
	-10 -5 1 CIG ACA CAG TOT COT GOT TOC TTA GOT GIVE TO FOR GGG CHG AGG GOO:	
•		1 <b>4</b> 4 337
	5 10 15	
35	ACC ATC TCA TAC AGG GCC AGC AAA AGT GTC ACT ACA TCT GGC TAY AGT.	. 192
	Thr Ile Ser Tyr Arg Ala Ser Lys Ser Val Ser The Ser Gly Tyr Ser	21
-	20 25 30 TAT ATG-CAC TOG AAC CAA CAG AGA CCA GGA CAG CCA AGA CTC CTC	340
	Tyr Met His Try Asn Gln Gln Arg Pro Gly Gln Pro Pro Arg Leu Leu	240
ю	35 40 45 50	٠.
	ATC TAT CTY GTA TCC AAC CTA GAC TCT GGG GTC CCT GCC AGG TTC AGT	
•	Ile Tyr Leu Val Ser Asn Leu Asp Ser Gly Val Pro Ala Arg Pha Ser	
	55 60 65 GGC AGT GGG ACA GAC ATC ACC CTC AAC ATC CAT CCT GTG GAG	₹ 23%
15		336 44 -
	70 75 80	
	GAG GAG GAT GCT GCA ACC TAT TAC TGT CAG CAC ATT GAG GGA GCT TAC	384
	Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ile Glu Gly Ala Tyr	.19
50	85 90 95	
	ACG TTC GGA GGG GGG ACC AAG CTG GAA ATA AAA	417
	Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys	
	200 103	

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	Sequence Listing	وي سنڌ ۾ مون سنڌ ۾ مون
_	Seq. I.D. number : 9	
5	Sequence length: 420	
	Sequence type : nucleic acid	
	Strandedness : double	
10	Topology : linear	
	Sequence kind : mRNA	· 12
	Original source	The second second
	Organism : mouse	4 4 9 7
15	Sequence characteristics	
	Symbol expressing characteristics : 0	DS
	•	4 (1.4 (1.5 A BC))
	Characteristics determination method	· S : Lots to the fig.
20	Symbol expressing characteristics.:	
	Presence position: 3190	
	Characteristics determination method	
25	Sequence  GCGGCCGCGG TGAGAACOFT TTGGGAATTC ATG GA	3 ACA CAG TCC CAG 48
		u Thr Gln Ser Gln
	-20	-15
	GTC TIT GTA TIC GTG TIT CTC TGG TIG TCT GGT)GT	
30	Val Phe Val Phe Val Phe Leu Trp Leu Ser Gly Va	
30	-10 :-5 GTG ATG ACC CAG TOTA CACARAGITC ATG TOO ACA TO	1 A GTA GGA GAC AGG 144
	Val Met ThroGin Ser His Lysophe Met Ser ThroSe	
	5 10	15
35	GTC AGT ATC ACC TGC AAG GCE AGT CAG GAT GTG AA	
	Val Ser Ile Thr Cys Lys Ala Ser Glm Asp Val As	_
	20 25 TGG TAT CAA CAG AAA CCA GGA CAA TCT CCT AAA CT	30 A CTG CTT TAC TCG 240
	Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Le	
40	35 40 4	5
	GCA TCC TAC CGG TAC ACT GGA GTC CCT GAT CAC TT	C ACT GGC AGT GGA 288
	Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp His Ph	e, Thr. Gly Ser. Gly
	50 55 60 TCT GGG ACG-GAT), TTC ACT, TTC ACG ATC AGC, GGT ,GTN	G CAG GCT GAA GAC 336
45	Ser Gly Thr. Asp Phe Thr Phe Thr Ile Ser Gly Va.	
••	70 75	, 80
	CTG GCA GTT TAT TAC TGT CAG CAA CAT TAT AGT CC	
	Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Pro	
50	95 90 (; ; ) GGT GCT GGG ACC AAG CTG GAA CTG AAA CGG GCT GAT	95 <u>-                                    </u>
50	Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp	
	100 105	
		•

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	Sequence Listing	
5	Seq. I.D. number: 10	
9	Sequence length: 360	
	Sequence type : nucleic acid	
	Strandedness : double	
10	Topology: linear	
	Sequence kind: mRNA	
	Original source	
	Organism : mouse	
15	Sequence characteristics	
	Symbol expressing characteristics : CDS * 14 10 10 10 10 10 10 10 10 10 10 10 10 10	-
	Presence position: 1360	
20	Characteristics determination method : S	: 1
	Symbol expressing characteristics : sig peptide	
	Presence position: 112	
	Characteristics determination methods: Specific	
25	Sequence	
	·	
	GGT GTT GAC GGA GAC ATT GTG ATG ACA CAG TCT CAC AAA TTC ATG TCC Gly Val Asp Gly Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser	48
	1 5 10	
30	ACA TCA GTT GGA GAC AGG GTC ACC ATC ACC TGC AAG GCC AGT CAG GAT	96
	Thr Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ale Ser Gln Asp	
	15 20 25 GTG ACT ACT GAT GTA GCC TGG TAT CAA CAG AAA CCA CGA CAA TCT CCT	
35	Val Thr Thr Asp Val Ala Trp Tyr Gln Gln Lys Pro Arg Gln Ser Pro	144
	30 35 Them. 400 satisfy	
	AAA CTA CTG ATT TAC TCG GCA TCC TAT CGG TAC ACT GGA GTC CCT GAT	192
	Lys Leu Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp	•
10	45 50 55 CGC TTC ACT GGC AGT GGA TCT GGG ACG GAT TTC ACCUATC AGC	240
	Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser	240
	60 65 70 75	
		288
15	Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr	
	80 85 90 AGT ACT GCG TGG ACC TTC GGT GGT GGC ACC AAG CTG GAA ATC AAA CGG	
	Ser Thr Ala Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arq	336
50	95 100 105 (105)	,
~		360
	Ala Asp Ala Ala Pro Thr Val Ser	•
	110	

.20

# SEQUENCE LISTING

5	(1) GENERAL INFORMATION:
	(i) APPLICANT:
	(A) NAME: HAGIWARA, Yoshihide
10	(B) STREET:4-14, Hiraisanso (C) CITY:Takarazuka-shi
	(D) STATE: Hyogo-ken
	(E) COUNTRY: Japan (F) POSTAL CODE (ZIP): none
15	(11) TITLE OF INVENTION: AMINO ACID SEQUENCES OF ANTI-IDIOTYPIC ANTIBODIES AGAINST ANTI-CANCER HUMAN MONOGLONAL ANTIBODY, AND DNA BASE SEQUENCES ENCODING THOSE SEQUENCES
20	(iii) NUMBER OF SEQUENCES:48
	(iv) COMPUTERS READABLE FORM:
	(A) MEDIUM TYPE:Floppy disk  (B) COMPUTER: IBM PC compatible
	(B) COMPUTER: IBM PC compatible (C) OPERATING SYSTEM: MS DOS 4.0
25	(D) SOFTWARE: Microsoft Word, Version 5.5
-	(v) CURRENT APPLICATION DATA: 04 115 683.8 (A) APPLICATION NUMBER: EP 94 115 683.8 (B) FILING DATE: October 5, 1994
30	the state of the s
	(2) INFORMATION FOR SEQ ID NO: 1:
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino acids
35	(B) TYPE amino acid
	(D) TOPOLOGY: linear (i) MOLECULE TYPE: protein or the protein of the second of the se
	(ix) FEATURE: (A) NAME/KEY:H-CDR1-1
	(A) NAME/KEY:H-CDR1-1 (D) OTHER INFORMATION:hypervariable region
40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:
	Ser Tyr Trp Met His
	5
	(2) INFORMATION: FOR USEQ: ID-NO: 2: SHE FINE SHEET SH
45	P
	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 5 amino acids  (B) TYPE: amino acid
	(D) TOPOLOGY: linear
50	(ii) MOLECULE TYPE:protein
	(A) NAME/KEY:H-CDR1-2
	(D) OTHER INFORMATION: hypervariable region
55	(xi) SEQUENCE DESCRIPTION:SEQ ID NO: 2:
<b>33</b>	

₹\* :

Asp Tyr Tyr Met Asn

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- 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 1965 (1967) - 
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5
                                   (2) INFORMATION FOR SEQ ID NO: 3:
                                                                                                                                                                        The second second
                                  (1) SEQUENCE CHARACTERISTICS:
                                                               (A) LENGTH:5 amino acids
                                            ٠.
                                                                     (B) TYPE:amino acid
                                                                     (D) TOPOLOGY:linear
10
                                  (ii)
                                                            MOLECULE TYPE:protein
                                                            FEATURE:
                                  (ix)
                                                                     (A) NAME/KEY:H-CDR1-3
                                                                     (D) OTHER INFORMATION: hypervariable region
                                                            SEQUENCE DESCRIPTION: SEQ ID NO: 3:
                                  (xi)
 15
                                  Asn Tyr Trp Met Gln
                                 (2) INFORMATION FOR SEQ ID NO: 4:

(1) SEQUENCE CHARACTERISTICS:
20
                                                (A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
                                                           MOLECULE TYPE: protein
                                  (ii)
                                                                   (A) NAME/KEY:H-CDR2-1
25
                                  (ix)
                                                           FEATURE:
                                                                    (D) OTHER INFORMATION: hypervariable region
                                                           SEQUENCE DESCRIPTION: SEQ ID NO: 4:
                                 (xi)
                                Ala Ile Tyr Pro Gly Asn Ser Asp Ile Ser Tyr Ser Gln Asn Phe Lys
30
                                                                                                                                                            Asp
                                 (2) INFORMATION FOR SEQ ID NO: 5:
                                                           SEQUENCE CHARACTERISTICS:
                                 (i)
35
                                                                   (A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
                                                          (ii)
                                                           FEATURE:
                                 (ix)
                                                                    (A) NAME/KEY:H-CDR2-2
(D) OTHER INFORMATION:hypervariable region
40
                                                           SEQUENCE DESCRIPTION: SEQ ID NO:5:
                                 (xi)
                                Phe Ile Arg Asn Lys Ala Asn Leu Tyr Thr Asp Tyr Ser Ala Ser
                                Val Lys Gly

(2) INFORMATION FOR SEQ ID NO: 6:
45
                                                          SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
                                 (1)
50
                                                                   (B) TYPE:amino acid
(D) TOPOLOGY:linear
                                 (ii)
                                                          MOLECULE TYPE:protein
                                                         FEATURE:
                                 (ix)
                                                                                                                                                 THE RESERVE AND THE PROPERTY OF THE PROPERTY O
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	(D) OTHER INFORMATION: hypervariable region	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:	
	Phe Ile Arg Asn Lys Ala Asn Tyr Tyr Thr Thr Glu Tyr Ser Ala Ser 5 10 15	
7	Val Lys Gly	•
• .	(2) INFORMATION FOR SEQ ID NO: 7:	
_	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH:17 amino acids (B) TYPE:amino acid	:
	(ii) MOLECULE TYPE:protein (ix) FEATURE:	
o	(A) NAME/KEY:H-CDR2-4 (D) OTHER INFORMATION:hypervariable region (xi) SEQUENCE DESCRIPTION:SEQ ID NO:7:	
	Ala Ile Tyr Pro Gly Asp Gly Asp Thr Arg Tyr Thr Glu Lys Phe Lys 5 10 15	
	41. MUNICOLONIA	Sat .
5	(2) INFORMATION FOR SEQ ID NO: 8: HE HOUSE TO (E)	
	(1) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 10 amino acids  (B) TYPE: amino acid	
0 <b>0</b>	(D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (ix) FEATURE:	
	(A) NAME/KEY:H-CDR3-1 (D) OTHER INFORMATION: hypervariable region (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:	£C.
<b>15</b>	Glu Glu Tyr Asp Tyr Asp Thr Leu Asp Tyr 10 10 10 15 15 15	
	(2) INFORMATION FOR SEQ ID NO: 9: The second of the second	Ejz
10	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH:11 amino acids  (B) TYPE:amino acid	:1-
45	(ii) MOLECULE TYPE: protein (ix) FEATURE:	<b>4.</b> 4
	(A) NAME/KEY:H-CDR3-2 (D) OTHER INFORMATION: hypervariable region (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:	
50	Asp Arg Gly Gly Arg Asp Trp Tyr Phe Asp Val	×
	(2) INFORMATION FOR SEQ ID NO: 10:	
	(i) SEQUENCE CHARACTERISTICS:	
55	·	i t

(A) LENGTH: 11 amino acids 22 (2)

```
(B) TYPE:amin acid
                  (D) TOPOLOGY:linear
         (ii)
                MOLECULE TYPE:protein
        (ix).
                FEATURE:
                  (A) NAME/KEY:H-CDR3-3
                  (D) OTHER INFORMATION: hypervariable region
                SEQUENCE DESCRIPTION: SEQ ID NO: 10:
        (xi)
10
        Asp Gly Phe Leu Arg Asp Trp Tyr Phe Asp Val
                                      10
        (2)
             INFORMATION FOR SEQ ID NO: 11:
15
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               (B) TYPE:amino acid
(D) TOPOLOGY:linear
MOLECULE TYPE:protein
        (ii)
20
                 (A) NAME/KEY:H-CDR3-4
        (ix)
               FEATURE:
                  (D) OTHER INFORMATION: hypervariable region
               SEQUENCE DESCRIPTION: SEQ ID NO: 11:
        (xi)
        Ser Gly Tyr Tyr Gly Ser Phe Val Gly Phe Ala Tyr
25
                          INFORMATION FOR SEQ ID NO: 12:
        (2)
        (i)
               SEQUENCE CHARACTERISTICS:
               (A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
MOLECULE TYPE: protein
FEATURE:
30
        (ii)
                 ATURE:
(A) NAME/KEY:L-CDR1-1
(D) OTHER INFORMATION:hypervariable region
               FEATURE:
        (ix)
35
               SEQUENCE DESCRIPTION: SEQ ID NO: 12: 35
        (xi)
        Tyr Arg Ala Ser Lys Ser Val Gln Leu His Leu Ala Ile Val Tyr Met
        His
             INFORMATION FOR SEQ ID NO: 13:
        (2)
               SEQUENCE CHARACTERISTICS:
        (i)
               (A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
MOLECULE TYPE: protein
FEATURE:
45
        (ii)
                 ATURE:
(A) NAME/KEY:L-CDR1-2
(D) OTHER INFORMATION:hypervariable region
        (ix)
50
               SEQUENCE DESCRIPTION: SEQ ID NO:13:
        (xi)
        Tyr Arg Ala Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser Tyr Met His 5 10 15
```

	(2) INFORMATION FOR SEQ ID NO: 14:	
5	(i) SEQUENCE CHARACTERISTICS:	
•	(A) LENGTH: 11 amino acids	
	(B) TYPE:amino acid	
٠.	(D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE: protein	
	(ix) FEATURE:	
10	(A) NAME/KEY:L-CDR1-3	
•	(D) OTHER INFORMATION: hypervariable region	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:	
	Lys Ala Ser Gln Asp Val Asn Thr Ala Val Ala	
15	5 10 10 10 10 10 10 10 10 10 10 10 10 10	
	the state of the s	
	(2) INFORMATION FOR SEQ ID NO: 15:	
	(i) SEQUENCE CHARACTERISTICS: (COT (C))	į.
20	(A) LENGTH: 11 amino acids and across	
	(B) TYPE:amino acid (D) TOPOLOGY:linear	
	(D) TOPOLOGY: linear	٠
	(ii) MOLECULE TYPE: protein (ix) FEATURE: (ix) (ix) FEATURE:	
	(A) NAME/KEY:L-CDR1-4	
	(D) OTHER INFORMATION: hypervariable region	٠:
25	(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:	
	Lys Ala Ser Gln Asp Val Thr Thr Asp Val Ala	•
	· E 10	
30	(2) INFORMATION FOR SEQ ID NO: 16:	•
	(i) SEQUENCE CHARACTERISTICS:	
	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 7 amino acids  (B) TYPE: amino acid	
	(B) TYPE:amino acid	
35	(D) , TOPOLOGY: linear many states and the state of the s	
	(ii) MOLECULE TYPE (protein	
	(1X) FEATURE:	
	(A) NAME/KEY:L-CDR2-1	
	(D) OTHER INFORMATION: hypervariable region	
40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:	٠٠;
	Iou Wal Com Aga Iou Clu Com	
	Leu Val Ser Asn Leu Glu Ser	
	(2) INFORMATION FOR SEQ ID NO: 17:	٠.
45	(2) INFORMATION FOR SEQ ID NOT 17:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 7 amino acids	
	(B) TYPE:amino acid	
	(D) TOPOLOGY: linear	۲
50	(ii) MOLECULE TYPE: protein	
30	(iv) Pramipp.	
	(A) NAME/KEY:L-CDR2-2	2
	(D) OTHER INFORMATION: hypervariable region	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:	**

*∞* 25

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Leu Val Ser Asn Leu Asp Ser
              (2) INFORMATION FOR SEQ ID NO: 18:
                    SEQUENCE CHARACTERISTICS:
              (i)
                      (A) LENGTH: 7 amino acids
                      (B) TYPE:amino acid
                      (D) TOPOLOGY:linear (CLECULE TYPE:protein
10
                    MOLECULE TYPE:protein
              (ii)
              (ix)
                    FEATURE:
                      (A) NAME/KEY:L-CDR2-3 :te 347
(D) OTHER INFORMATION:hypervariable region
                    SEQUENCE DESCRIPTION: SEQ ID NO: 18:
              (xi)
15
             Ser Ala Ser Tyr Arg Tyr Thr
                                              age of the Book Hills to
             (2) INFORMATION FOR SEQ ID NO: 19:
20
             (i)
                    (A) LENGTH:8 amino acids
(B) TYPE:amino acid (C) TOPOLOGY:linear (C)
                    MOLECULE TYPE:protein
FEATURE:

(A) NAME/KEY:L-CDR3-1

(D) OTHER INFORMATION:hypervariable region
             (ii)
25
             (ix)
             (xi)
                    SEQUENCE DESCRIPTION: SEQ. ID NO: 10: 11 1/4 (1)
                      Gln His Ile Arg Val AlanTyr Thrank 18 1 4 707 1 4 1 4 1
30
                                      HAT ON THE WAY THE WAY THE
             (2) INFORMATION FOR SEQ ID NO: 20:
                    SEQUENCE CHARACTERISTICS: To part the Following the con-
             (1)
                      (A) LENGTH: 8 amino acids
(B) TYPE: amino acids
35
                           TYPE:amino acide 5210 Fab. 16 AND 10 48.78
                      (D) TOPOLOGY: linear ( ) Fig. 18 (17) 2 (5)
                    (ii)
             (ix)
                      (A) NAME/KEY: L-CDR3-2- TENT 12 - Y 18 - 20 1 25 1
                      (D) OTHER INFORMATION: hypervariable region
                    SEQUENCE DESCRIPTION: SEQ ID NO: 20: 100 TELEPIONE
             (xi)
             45
                  INFORMATION FOR SEQ ID-NO: 21:
             (2)
             (i)
                    SEQUENCE CHARACTERISTICS:
                      QUENCE CHARGETHING AGIDS

(A) LENGTH: 8 amino acids
                   (B) TYPE:amino acid
(D) TOPOLOGY:linear
MOLECULE TYPE:protein
             (ii)
             (ix)
                    FEATURE:
                      (A) NAME/KEY:L-CDR3-3
                      (D) OTHER INFORMATION: hypervariable region
```

```
(xi)
                                   SEQUENCE DESCRIPTION: SEQ ID NO:21:
                  Gln His Ile Glu Gly Ala Tyr Thr
                  (2)
                              INFORMATION FOR SEQ ID NO: 22:
                  (i)
                                   SEQUENCE CHARACTERISTICS:
10
                                        (A) LENGTH:9 amino acids
                                                   TYPE:amino acid
                                        (B)
                                        (D) TOPOLOGY: linear
                  (ii)
                                   MOLECULE TYPE:protein
                 (ix)
                                   FEATURE:
                                        (A) NAME/KEY:L-CDR3-4
15
                                        (D) OTHER INFORMATION: hypervariable region
                                   SEQUENCE DESCRIPTION: SEQ ID NO: 22:
                  (xi)
                 Gln Gln His Tyr Ser Pro Pro Leu Thr
                                                                                 LD NO. 23:
20
                           INFORMATION FOR SEQ ID NO: 23:
                  (2)
                                                                                                        inter and
                                  SEQUENCE CHARACTERISTICS:
                  (i)
                                       (A) LENGTH: 9 amino acids 100 0000
                                                   TYPE:amino acid
                                       (B)
                                       (D) TOPOLOGY: linear
25
                                  MOLECULE TYPE:protein a Gue UNAGOWA
                  (ii)
                                  FEATURE : Livevier M. PANCOFF & RELIE
                 (ix)
                                       (A) NAME/KEY:L-CDR3;5 : ANTENTE AND DEPOSITE AND
                                        (D) OTHER INFORMATION: hypervariable region
                                  SEQUENCE DESCRIPTION: SEQ ID, NO:23: 11
                 (xi)
                 Gln Gln His Tyr Ser Thr Ala Trp Thr
                                                                                   THE THE SECTION TO MAKE IN
                                                           5
                            INFORMATION FOR SEQ ID NO: 24: 24.2 For the September 5
                 (2)
                                  SEQUENCE CHARACTERISTICS: La con service de la constant de la cons
35
                 (i)
                                       (A) LENGTH: 34 base pairs and pairs
                                       (B) TYPE:nucleic acid presonating the call
                                       (C) STRANDEDNESS:single
                                  (D) TOPOLOGY:linear (COLOR DE LA CALLA DE
                  (11)
40
                 (iv)
                 (iii)
                                  HYPOTHETICAL: no
                 (ix)
                                  FEATURE:
                                       ATURE:
(A) NAME/KEY:H Leader Sequence A
                                                   OTHER INFORMATION: R is A or G;
                                                                                  K is G or T;
45
                                                                                                Y is C or T;
                                                                                                M.is.A or C.
                                  SEQUENCE DESCRIPTION: SEQ ID NO. 24:
                 (xi)
                GGGAATTCAT GRASTTSKGG YYTMARCTKG RTTT
50
                                                                                                                                                                                     34
                             INFORMATION FOR SEQ ID NO: 25: SEQUENCE CHARACTERISTICS:
                 (2)
                 (i)
```

7:

5	(iii)	(A) LENGTH:34 bas pairs (B) TYPE:nucl ic acid (C) STRANDEDNESS:single (D) TOPOLOGY:linear MOLECULE TYPE:cDNA HYPOTHETICAL:no	
10	(iv) (ix)	ANTISENSE: no FEATURE:  (A) NAME/KEY: H Leader Sequence B  (D) OTHER INFORMATION: S is C or G;  Y is C or T;	
15		W is A or T; R is A or G. SEQUENCE DESCRIPTION:SEQ ID, NO:25:	
		CAT GRAATGSASC TGGGTYWTYC TCTT FORMATION FOR SEQ ID NO: 26:	34
20	(i)	SEQUENCE CHARACTERISTICS:  (A) LENGTH:18 base pairs  (B) TYPE:nucleic acid  (C) STRANDEDNESS:single  (D) TOPOLOGY:linear	.,
<i>2</i> 5	(ii) (iii) (iv) (ix)	MOLECULE TYPE:cDNA HYPOTHETICAL:no ANTISENSE:no FEATURE: (A) NAME/KEY:H Leader Sequence C	•
30	(Xi)	SEQUENCE DESCRIPTION: SEQ ID, NO: 26:	_
		FORMATION FOR SEQ ID NO: 27:	.8
35	(i)	SEQUENCE CHARACTERISTICS:  (A) LENGTH: 35 base pairs  (B) TYPE:nucleic acid  (C) STRANDEDNESS:single  (D) TOPOLOGY:linear	:
40	(ii) (iii) (iv) (ix)	MOLECULE TYPE:cDNA HYPOTHETICAL:no ANTISENSE:no FEATURE: (A) NAME/KEY:H Constant Region	
45	(xi)	(D) OTHER INFORMATION:R is A or G;  K is G or T; N = 100   1	
•		TTC CAGGGRCCAR KGGATARACN GRTGG	5
50	(2) II (i)	FORMATION FOR SEQ ID NO: 28: SEQUENCE CHARACTERISTICS: (A) LENGTH:32 base pairs (B) TYPE:nucleic acid (C) STRANDEDNESS:single	
		(D) TOPOLOGY: linear	

	(ii)	MOLECULE TYPE:cDNA
	(iii)	HYPOTHETICAL:no
:	(iv)	ANTISENSE: no
•	(ix)	FEATURE:
		(A) NAME/KEY:L Lead r Sequence A
		(D) OTHER INFORMATION:R is A or G:
		K is G or T;
	•	W is A or T;
0	*	Y is C or T.
•	1 m 2 \	SEQUENCE DESCRIPTION: SEQ ID NO: 28:
	(XI)	SEQUENCE DESCRIPTION. SEQ 15 No. 20.
	i	TCAT GRAGWCACAK WCYCAGGTCT TT 32
	GGGAAT	TCAT GRAGWCACAK WCYCAGGTCT TT 32
	40.	NFORMATION FOR SEQ ID NO: 29:
5	(2) I	NFORMATION FOR SEQ ID NO. 23.
		GROUPINGE CUADACTERICS.
	(i)	SEQUENCE CHARACIERISTICS.
		(A) LENGTH: 33 base pairs
		(B) Type:nucleic acid
		(C) STRANDEDNESS:single
20		(D) MODOLOGY-linear
	(ii)	WOLDSTEE BUILD ADMA
	(iii)	HYPOTHETICAL: no
	(111)	ANTISENSE: no
	(iv)	FEATURE:
	(ix)	(A) NAME/KEY:L Leader Sequence B
5		SEQUENCE DESCRIPTION: SEQ ID NO: 29:
	(xi)	SEQUENCE DESCRIPTION: SEQ ID NO. 23.
		CART CCAGACAGAC ACACTCCTGC TAT
	GGAATI	CAMI GONONCHONO MONOCONTRA MANAGEMENTO
	. •	the control of the co
	(2) I	NFORMATION FOR SEQ ID'NO: 30:
30		The state of the s
	(i)	SEQUENCE CHARACTERISTICS:
		(A) LENGTH: 30 base pairs
		(B) TYPE:nucleic acid
		(C) STRANDEDNESS: single
		(D) TOPOLOGY:linear
35	(ii)	MOLECULE TYPE:CDNA
	/444	HYPOTHETICAL: no
	(iv)	FEATURE:
	(ix)	(A) NAME/KEY:L constant
		SEQUENCE DESCRIPTION: SEQ ID NO: 30:
10	(xi)	SEQUENCE DESCRIPTION: SEQ 1D NO. 30.
		30
•	CCCAAC	CTTA CTGGATGGTG GGAAGATGGA
	(2)	INFORMATION FOR SEQ ID NO: 31:
45	(i)	SEQUENCE CHARACTERISTICS:
	• •	(A) LENGTH:357 base pairs
		(B) TYPE: nucleic acid ( 2007 ) 200 ( 2007 ) ( 2007 ) ( 2007 )
		(C) STRANDEDNESS: double
		(D) TOPOLOGY: linear and Control of the Control of
	(ii)	MOLECULE TYPE:mRNA
50	(iii)	HYPOTHETICAL: no
		ANTISENSE: no
	(iv)	1414 10010 111
	(vi)	
		(A) CHOANTELLIAME TO
	(ix)	FEATURE:
55		

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	(x)		SEQU	l) JENCE	NAME/ E DES	KEY: CRIP	Idio TION	3 H :SEO	cha	in v	aria 31·	ble/	Idio	17	H ch	ain	varia	ble
5																		
	Gl	Va.	r CAC	Lev	GIU	Gln	Ser	GGG	Thr	Val 10	Leu	GCA Ala	AGG	Pro	GGG Gly 15	GCT Ala	48	
10	TCA Ser	. va.	3 AAG L Lys	Mer	Ser	TGC Cys	AAG Lys	GCT Ala	TCG Ser 25	GGC Gly	TAC Tyr	ACC Thr	TTT	AAC Asn 30	AGC	TAC Tyr	96	
15	TGG Trp	met	CAC His	TIP	⊳ va∓	. Lys	GIn	Arg	Pro	GGA Gly	CAG Gln	GGT	CTG Leu 45	GAA gGlu	TGG	ATT	144	
	GGC Glý	-ATG	: ATT	Tyr	Pro	₄GIV	AAT Asn 55	AGT Ser	GAT Asp	ATT Ile	AGC Ser	TAC Tyr 60	AGC Ser	CAG Gln	AAC Asin	TTT Phe	192	
20	AAG Lys 65	GAC Asp	AGG Arg	GCC Ala	AAA Lys	CTG Leu 70	ACT Thr	GCC Ala	GTC Val	Thr	TCC Ser 75	ACC Thr	AGC Ser	ACT	GCC	TAC Tyr 80	240	
25	ATG Met	GAA Glu	CTC Leu	AGA Arg	AGC Ser 85	CTG Leu	ACA Thr	AAT Asn	GAG. Glu	GAC Asp 90	Ser'	Ala	GTC Val	Tyr	TTC Phe 95	TGT Cys	288	·
	ACA Thr	AAA Lys	GAG Glu	GAA Glu 100	TAT Tyr	GAT Asp	TAC Tyr	GAC Asp	ACC Thr 105	Leu	GAC Asp	TAC	Trp	Gly	CAA Gln	Gly	336	
30 ·	ACC Thr	TCA Ser	GTC Val 115	ACC Thr	GTC Val	TCC Ser	TCA Ser		٠.	•				71. জীট ভা ়াজ শুৰু			357	
	(2)	IN	FORM	ATIO	N FOI	R SĘÇ	İD	NO:	32:	, ·						•		
35	(i)		SEQUI (A (B (C	ENCE ) Li ) T	CHAI ENGTI YPE: 1 TRANI	RACTE 1:366 nucle DEDNE	RIST bas ic a	ICS: e pa cid loub!	irs.		n '-		ata O		e . Vo La CA			
10	(ii) (iii (iv) (vi)	L) .	(D) MOLE HYPO ANTIS ORIG	CULE CHET SENSI	TYPS ICAL: E:no	no	IA ,-		. 4	<b>7</b> *	× .	• · · · · · · · · · · · · · · · · · · ·				, , , , , , , , , , , , , , , , , , , ,	- - · · ·	
ı <b>š</b>	(ix)	j	(A)- FEAT( (A)	JRE:	AME/F	ΈΥ: I	dio	20 H	I cha	in v	eria	ble		•		• •	,	
•	(xi)	, ;	SEQUI	ENCE	DESC	RIPT	'ION:	SEQ	ID N	0: 3	2:	٠٠,	٠.			~	٠.	
·	GAĞ Glu	GTG Val	AAG. Lys	CTG	GTG	GAG	TCT	GGA	GGA	GGC	TTG	<b>GTA</b>	CAG Gln	CCT Pro	GGG Gly 15	GGT Gly	48	
5 <b>0</b> ·	TCT Ser	CTC Leu	AGA Arg	CTC Leu 20	TCC Ser	TGT Cys	GCA Ala	Thr	TCT Ser 25	GGG Gly	TTA Leu	ACC Thr	TTC Phe	ACT Thr 30	GAT Asp	TAC Tyr	96	

5	TAC	ATG Met	AAC Asn 35	TGG	Val	Arg	CAG Gln	CCT Pro 40	CCA Pro	GGA Gly	AAG Lys	GAA Glu	CTT Leu 45	GAA Glu	TGG	TTG Leu	144
is:	GGT Gly	TTT Phe 50	ATT	AGA Arg	AAC	AAA Lys	GCT Ala 55	AAT Asn	CTT Leu	TAC Tyr	ACA Thr	ACA Thr 60	GAC Asp	TAC Tyr	AGT Ser	GCA Ala	192
10	TCT Ser 65	GTG Val	AAG Lys	GGT Gly	CGG Arg	TTC Phe 70	ACC Thr	ATC Ile	TCC Ser	AGA Arg	CAT Asp 75	AAT Asn	.CCC Pro	Gln	Ser	Ile 80	240
15	CTC Leu	TAT Tyr	CTT Leu	CAA Gln	ATG Met 85	AAC Asn	ACC Thr	CTG Leu	ACA Thr	Thr 90	Glu	Asp	Ser	GCC Ala	ACT. Thr. 95	TAT	288
	TAC Tyr	TĜT Cys	GCA Ala	AGA Arg 100	GAT Asp	AGG Arg	GGG	GGG Gly	AGG Arg 105	GAC	TGG Trp	TAC	TTC	GAT	GTC	TGG:	@7 # <b>336</b> € &
20	GGC Gly	ATG	GGG Gly 115	ACC	ACG Thr	GTC Val	THE.	GTC Val 120	TCC Ser	TCA Ser							366) 366)
25	(2) (1)		SEQUI (A) (B)	ENCE ) Li ) Ty	CHAF ENGTH YPE: 1	ACTE 1:366 pcle	ID RIST bas ic a	ICS: e pa cid	irs			73 ±2	14 m			ye i	
3 <b>0</b>	(ii (ii (iv (vi	) 1 L) H	ORIGI	) TO CULE THET SENSI INAL	TYPE TYPE CAL: : no SOUR	GY! I ::mRN :no :CE:	inea IA	ir "'	· ·		i :		. ,		20 Jn		
: 35	(ix)	) 5	SEQUI	JRE: ) NA ENCE	AME/K DESC	EY: I	:NOI	27 H SEQ	ID N	IO: _3	varia 13:	ទេធមួ	ing A	:.	errer		
	GAG Glu	GTG Val	AAG Lys	CTG Leu	GTG Val 5	GAG Glu	TCT Ser	GGA Gly	GGA Gly	GGC Gly 10	TTG Leu	۷a۱,	CAG Gln	Pro	GGG Gly 15	GGT	48
40	TCT Ser	CTG Leu	AGA Arg	CTC Leu 20	Ser	Cys	Ala	Thr	Ser	Gly	TTC Phe	Thr	Phe 0	Thr 30	GAT Asp	ΪĀτ	<b>96</b> .
45	TAC Tyr	ATG Met	AAC Asn 35	TGG Trp	GTC Val	Arg	CAG Gln	Pro	Pro	Gly	AAG Lys	GCA	CTT	GAG Glu	TGG	TTG Leu	144
*	GGT Gly	Phe.	ſle	AGA Arg	Asn	Lys	Ala	TAA neA	TAT Tyr	TAC	ACA Thr	Thr	Glu '	TAC Tvr	AGT	GCA Ala	

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5	H., S E	GTG Val	AAG Lys	GGT Gly	CGG Arg	TTC Phe 70	ACC Thr	ATC Ile	TCC S r	AGA Arg	GAT Asp 75	AAT Asn	TCC S r	CAA Gln	AGC Ser	ATC Ile 80	240
	CTC Leu	TAT	CTT Met	CAA Asn	ATG Thr 85	AAC Leu	ACC Thr	CTG Leu	AGA Arg	GCT Ala 90	Glu	GAC Asp	AGT Ser	GCC Ala	ACT Thr 95	TAT Tyr	288
10	TAC Tyr	TGT Cys	GCA Ala	AGA Arg 100	GAT Asp	GGG Gly	TTC Phe	CTA Leu	CGG Arg 105	Asp	TGG Trp	TAC Tyr	TTC Phe	GAT Asp 110	GTC Val	TGG Trp	336
15	GGC Gly	GCA Ala	GGG Gly 115	ACC Thr	ACG Thr	GTC Val	ACC Thr	GTC Val 120	TCC Ser	TCA Ser				•	·. '		366
	(2)	IN	FORM	ATION	N FOI	R SEC	Q ID	NO:	34:	3			٠.		*		. ,
<b>20</b>	( <b>i</b> )		(B)	LE TY	engti (Pe : 1 (Rani	1:363 nucle DEDNE	baseic a	se pa cid loub	airs le	- 8	<u>.</u>						
25	(ii) (ii) (iv)	L) 1	(D) MOLE HYPOT ANTIS ORIGI	CULE THETI SENSE	TYPE CAL:	no	IA.							·		•	γ.
	(ix)	· ) 1	(A) FEATU	OF JRE: NA	rgani Me/f	SM:n (Ey:1	ouse	33 E	i cha	ain v	aria	bla	21. 1		,		
<b>30</b>	GAG	GTT	CAG Gln	CTC	CAG	CAG Gln	TCT	GGG Gly	GCT Ala	GAA	CTG	GCA	AGA	CCT Pro	GGG Gly 15	GCT Ala	•
3 <b>5</b>	TCA Ser	Val.	AAC Asn	Leu	Ser	TGC Cys	AAG Lys.	GCT	Ser	GGC Gly	TAC Tyr	ACC Thr	TTT Phe	ACT Thr 30	AAC Asn	TAC	96 451
40	TGG	Met	CAG Gln 35	TGG Trp	GTA Val	AAA Lys	CAG Gln	Arg	CCT Pro	GGA Gly	CAG Gln	GGT Gly	CTG Leu 45	GAA Glu	Trp	ATT Ile	144
	Ğly	GCT Ala 50	ATT Ile	TAT Tyr	CCT Pro	GGA Gly	Asp 55	Gly	Asp	Thr	Arg	TAC Tyr 60	ACT Thr	CAG Gln	AAG Lys	TTC Phe	192
45	Lys 65	GLY		GCC Ala	Thr	TTG Leu 70	Thr	Ala	GCT Ala	Lys	Ser 75	TCC Ser	Ser	ACA Thr	Ala	TAC Tyr 80	240
50	ATG	CAA	CTC Leu	ACC Ser	AGC	TTG	GCA Ala	TCT	GAG Glu	GAC	TCT Ser	GCG Ala	GTC	TAT Tyr	TAC	TGT	288
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5	Ala Arg Ser Gly Tyr Tyr Gly S r Phe Val Gly Phe Ala Tyr Trp Gly 100 105 110	6
	CAA GGG ACT CIG GTC ACT GTC TCT GCA Gln Gly Thr Leu Val Thr Val Ser Ala 115 120	3
10		
	(2) INFORMATION FOR SEQ ID NO: 35:	
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 336 base pairs	
15	(B) TYPE:nucleic acid (C) STRANDEDNESS:double	
	(D) TOPOLOGY:linear (ii) MOLECULE TYPE:mRNA	
	(iii) HYPOTHETICAL:no	
	(iv) ANTISENSE: no	
20	(vi) ORIGINAL SOURCE: (A) ORGANISM:mouse	
•	(ix) FEATURE:	٠
	(A) NAME/KEY:Idio 3 L chain variable (xi) SEQUENCE DESCRIPTION:SEQ ID NO: 35:	
2 <b>5</b> .	GAC ATT GTG CTG ACA CAG TCT CCT GCT TCC TTA GCT GTA TCT CCT CTG 4 Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Pro Leu	8
	Asp lie val Led the Gin Set Flo Ala Set Led Ala val Ser Fro Led  5 10 15 15	
		6
30	Gly Gln Arg Ala Thr Ile Ser Tyr Arg Ala Ser Lys Ser Val Gln Leu 20 25 30	
	ကြုံများကြုံသည်။ ကြုံရှိသည်။ အများသည်။ ကျော်သည် ကြိုကြောက်သည်း ကြိုင်းမြောက်သည် မြောကြာသည်။ မြောက်သည် မြောက်သည မြောက်သည်	_
	CAT CTG GCT ATA GTT TAT ATG CAC TGG AAC CAA CAG AAA CCA GGA CAG 14 His Leu Ala Ile Val Tyr Met His Trp Asn Gln Gln Lys Pro Gly Gln	4
	8 200 076 THE BOT LA 200 000 BOT BEA SO .45 . WITHER DN . 600	
35	CCA CCC AGA CTC CTC ATC TAT CTT GTA TCC AAC CTA GAA TCT GGG GTC 19	2
	Pro Pro Arg Leu Leu Ile Tyr Leu Val Ser Asn Leu Glu Ser Gly Val	_
	$\sim$ 50 box $\ell$ is two that $25$ or tho that by $160$ $\ell$ in the $\ell$	
	CCT GCC AGG TTC AGT GGC AGT GGG TCT GGG ACA GAC TTC ACC CTC AAC 24	0
40	Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn 65	
	ATC CAT CCT GTG GAG GAG GAT GCT GCA ACC TAT TAC TGT CAG CAC 28  Ile His Pro Val Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His	8
	and the control of th	
45	ATT AGG GTA GCT TAC ACG TTC GGA GGG GGG ACC AAG CTG GAA ATA AAA 33	_
	Ile Arg Val Ala Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys	9
•	- 1876 - 1885 - 1885 - 1990	
	ကြည်း ကြန်း၍ သို့ကောင်များ သည်။ သည်။ သည်။ သည်။ သည်။ သည်။ သည် ကြန်းသည်။ လည်း လည်း ကြန်းသည်။ လည်း ကြန်းသည်။ မြောင်း	
50	(2) INFORMATION FOR SEQ ID NO: 36:	
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 330 base pairs	

·- 33

## EP 0.702.082 A1

	(C) STRANDEDNESS: double	
5	(D) TOPOLOGY:linear	
•	(11) MOLECULE TYPE:mRNA	
	(iii) HYPOTHETICAL:no	
	(iv) ANTISENSE:no	•
	(vi) ORIGINAL SOURCE:	,
	(A) ORGANISM:mouse	
10	(ix) FEATURE:  (A) NAME/KEY: Idio 17 L chain variable	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:	•
	GAC ATT GTG CTG ACA CAG TCT CCT GCT TCC TTA GCT GTA TCT CTG GGG	8
	Len Tie Val Leir Thr Gin Ser Pro Ala Ser Leu Ala Val-Ser Leu Giv.	/ · ·
15		٠
	De la	
		6
	Gin Arg Ala Ser Ile Ser Tvr Arg Ala Ser Lvs Ser Val Ser Thr Ser	Æ.
	25 25 25 25 25 25 25 25 25 25 25 25 25 2	ť,
20		
	GGC TAT AGT TAT ATG CAC TGG AAC CAA CAG AAA CCA GGA CAG CCA CCC 14	4
	Gly Tyr Ser Tyr Met His Trp Asn Gln Gln Lys Pro Gly Gln Pro Pro	
	7 45 45 A	•
	AGA CTC CTC ATC TAT CTT GTA TCC AAC CTA GAA TCT GGG GTC CCT GCC 19	12
oe.	and the Lee The Pur Lee Val Ser Asn Lee Glu Ser Gly Val Pro Ala	1
25	Arg Leu Leu Ile Tyr Leu Val Ser Asn Leu Glu Ser Gly Val Pro Ala	:
	fr for the second secon	
		10
	Arg Phe Ser Glv Ser Glv Ser Glv Thr Asp Phe Thr Leu Asn Ile His	
	65 70 75% ( ) #0% MONTARAD80)	
30		
		38
	Pro Val Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gla His Ile Arg	
	85 90% % *********************************	
		30
35	Gly Ala Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys	
	100 105 CHE 1245 110 M.	
		1
	STATE A STATE OF THE STATE OF T	•
	(2) INFORMATION FOR SEQ ID NO: 37:	
40	2.9 (27) (3)	
	(i) SEQUENCE CHARACTERISTICS:	
	(U) Devotion and business	
	(R) TYPE:nucleic acid (C) STRANDEDNESS:double	-
	(C) STRANDEDNESS:double (D) TOPOLOGY:linear	
45	(ii) MOLECULE TYPE:mRNA	
	(iii) HYPOTHETICAL:no	
	(iv) ANTISENSE:no	.£.:
	(vi) ORIGINAL SOURCE:	1
	(A) ONGANIBITING	
	/ ( PPAMIDE.	
50	(A) NAME/KEY: Idio 20 L chain variable	•
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:	

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															Leu		40
5	•				5					10					15	- 4 T	
															ACA Thr		.96
		<u> </u>		20					25					30	(/		
10															CCA Pro		144
	-		35	IYL			_	40		<b>3</b> . • •	, nieg	110	45	رييد	, <u>.</u>	FILO	åæ.
	AGA	CTC;	CTC	ATC	TAT	CTT	GTA.	TÇC	AAC	CTA	GAC	TÇT	GGG	GTC	CCT	GCC .	192
15	Arg	50			_	Leu	55			Leu	Asp	Ser 60	GIY	Val	Pro	Ala	
	AGG	TTC	AGT	GGC	AGT	GGG	TCT	GGG	ACA	GĄČ	TTC	ACC	CTC	AAC	ATC	CAT .	240
	Arg 65	Phe	Ser	Gly;	Ser	Gly 70	Ser	Gly	Thr	<sub>"</sub> Ašp	Phe 75	Thr	Leu	Asn	Ile	His" 80	••
20	CCT	GTG	GAG	⊝ ⟨ <b>GAG</b>	GAG	GAT	GCT,	GCA	ACC	TAT	TAC	TGT	CAG	CAC	ATT	GAG	288
	Pro	Val	Glu	Glu	G112 85	,Asp	Ala	Ala	Thr	Tyr 90	Tyr	Cys	Gln	His	'I l'e 95	Glu '	• • •
	GGA	CCT	CC DATE	ACG.	TTC	GGΛ	GGG	GGG	ACC	AAG	CTG	GAA	ATA	AAA	ران در. د کافر در.		330
25	Gly	Ala	Tyr	Thr 100	Phe	Gly	Gly	Gly	Thr 105	Lys	Leu	gGlu	Ile	Lys 110	)1.		9.0
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			(B)	) T	PE:	uncte	31C 9	3C1Q	;	· · · · ·	• • •	ತ ಟ್ಫಾಚ	%	 :	` .	, ,	
			(C) (D)	) TO	POL	OGY ; .	ESS: d	ır			) <u>,</u> 1,					. 55	٠.
35	(ii)	) 1 i) 1	MOLE( HYPO'	CULE	TYP	Z:mR	XA;		10	· .							•
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40	(ix	•	FEATI ( A	) N.			Idio					able		٠. ا			
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	GAC	ATT	GTG	ATG	ACC	CAG	TCT	CAC	AAA	TTC	ATG	TCC	ACA	TCA	GTA Val	GGA Glv	48
•	Asp	116	vaı	Mec	5	GIII	Ser	urs	пуэ	10	Mec	Per			. 15	5.	: 443
45	GAC	AGG	GTC	AGT	ATC	ACC	TGC	AAG	GCC	AGT	CAG	GAT	GTG		ACT		96
	Asp	Arg	Val	Ser 20	Ile	Thr	Cys	Lys	Ala 25	Ser	Gln	Asp	val	Asn 30	Thr	ALA	(4)
<b>5</b> 0	GTA	GCC	TGG	TAT	CAA	CĄG	AAA	CCA	GGA	CAA	TCT	CCT	AAA	CTA	CTG	CTT	144
50	Val	Ala	Trp 35	Tyr	Gln	Gln	Lys	Pro 40	Gly	Gln	Ser	.Pro	Lys 45	TET	Leu	: Leu	()

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5	TAC	TCG Ser 50	GCA Ala	TCC Ser	TAC Tyr	CGG Arg	TAC Tyr 55	ACT Thr	GGA Gly	GTC Val	CCT Pro	GAT Asp 60	CAC His	TTC Phe	ACT Thr	GGC Gly	192
	AGT Ser 65	GGA Gly	TCT Ser	GGG Gly	ACG Thr	GAT Asp 70	TTC Phe	ACT Thr	TTC Ph	ACC Thr	ATC Ile 75	AGC	GGT Gly	GTG Val	CAG Gln	GCT Ala 80	240
10	GAA Glu	GAC Asp	CTG Leu	GCA Ala	GTT Val 85	TAT Tyr	TAC Tyr	TGT Cys	CAG Gln	CAA Gln 90	CAT His	TAT	AGT Ser	CCT Pro	CCT Pro 95	CTC Leu	288
15	ACG Thr	TTC	GGT Gly	GCT Ala 100	GGG	ACC Thr	AAG Lys	CTG Leu	GAA Glu 105	CTG Leu	AAA Lys	:				· · · .	321
	(2)	IN	FORM	ATIO	I FOF	R SEC	) ID	NO:	39:		:				• • • • • • • • • • • • • • • • • • • •		
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	(ix)		(A) JTAET	JRE:			. /	· 204	<i>=</i>	iin v		. 14 Y	Auge.				.,
30	(xi)	( D	EQUE									rőte	141.5		7	···•;	
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<b>35</b>		AGG Arg															ੂਨੂ <b>96</b> ਜੁਲ੍ਹ
40	GTA Val	ĢCC Ala	TGG Trp 35	TAT Tyr	CAA Gln	CAG GĻņ	Lys	CCA Pro 40	CGA Arg	CAA Gln	TCT Sér	CCT Pro	AAA Lys 45	CTA Lêu	CTG Ļeu	ATT Ile	144
	TAC Tyr	TCG Ser 50	GCA Ala	TCC Ser	TAT Tyr	CGG Arg	TAC Tyr 55	ACT The	GLY GGA	GTC Val	CCT Pro	GAT Asp 60	CGC	TTC Phe	ACT Thr	GGC Gly	ர <b>,192</b> ¤ா
45		GGA Gly															240
<b>50</b> .	GAA Glu	GAC Asp	CTG Leu	GCA Ala	GTT Val 85	TAT Tyr	TAC Tyr	TGT Cys	CAG Gln	CAA Gln 90	CAT His	TAT Tyr	AGT Ser	ACT Thr	GCG Ala 95	Trp	_ <b>288</b>

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5	ACG T	PTC Phe	GGT Gly	GGT Gly 100	GGC Gly	ACC	AAG Lys	CTG Leu	GAA Glu 105	Ile	Lys	•					321
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	(2) <sup>f</sup>	IÑF	ORMA	TION	FOR	SEÇ	] ID	NO:	40:			;	•			• • •	71.5 7.7
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15	(ii) (iii) (iv) (vi)	) H A	YPOT NTIS	ULE HETI ENSE	TYPE CAL:	:mRN no	linea IA	er 	* **				¥1.	***		r. ∰ ₹	20 . 4 90
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20	(xi)		(A)	N.A			lone			10 : 4 C	):		i ja Marka	3.7% :4%		,	63
	CTG 7	rcg Ser	GTA Val	ACT Thr	TCA Ser -5	GGG Gly	GTC Val	TAC Tyr	TCA Ser	GAG Glu 1	Val	CAG Gin	Leu	GAG Gln 5	CAG Gln	TCT Ser	·48
25	GGG A	ACT Thr	GTG Val 10	CTG Leu	GCA Ala	AGG Arg	CCT Pro	GGG Gly 15	GCT Ala	Ser	GTG Val	AAG Lys	ATG	TCC	TGC Cys	AAG Lys	96
30	GCT 1	rcg Ser 25	GGC Gly	TAC Tyr	ACC Thr	TTT Phe	AAC Asn 30	AGC	TAC Tyr	TGG Trp	ATG Met	CAC His 35	TGG Trp	GTA Val	AAA Lys	CAG Gln	144
	AGG (Arg 1	Pro	GGA Gly	CAG Gln	GGT Gly	CTG Leu 45	GAA Glu	TGG Trp	ATT, Ile	GGC GIY	GCG Ala 50	ATT Ile	TAT Tyr	CCT Prò	GGA Gly	AAT Asn 55	192
<b>35</b>	AGT (	GAT Asp	ATT Ile	AGC Ser	TAC Tyr 60	AGC Ser	CAG Gln	AAC Asn	TTT Phe	ÁAG Lys 65	GĂĈ Asp	AGG Arg	GCC Ala	AAA Lys	CTG Leu 70	ACT Thr	240
40	GCC (	GTC Val	ACA The	TCC Ser 75	ACC Thr	AGC Ser	ACT Thr	GCC Ala	TÁC Tyr 80	ATG Met	GAA Glu	CTC	AGA Arg	AGC Ser 85	CTG Leu	ACA	288
45	AAT ( Asn (	GAĞ Glü	GAC	TCT	GCG Ala	GTC Val	ŢĂŢ Tyr	TTC Phe 95	ŤGŤ Cys	AÇA Thr	AAA Lys	GĀĢ Glú	GAA Glu 100	TAT Tyr	GAT Asp	TAC Tyr	336
		Thr 105	Ľeu	Asp	Tyŕ	Trp	Gly 110	Gln	Glý	Thr	Ser	Vaļ 115	Thr	Val	ser	Ser	384
50	GCC Ala 1	AAA Lys	ACG Thr	ACA Thr	ČCC Pro	21.	*		\$3.5 T	i vi F	3.9	2 V	19. 13.1 24	£;∤	5 MM 4 - 1	*, *	399

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5	(i)		SEQU	ENCE	CHA	RACT	ERIS'	TICS	:			··· i					
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10	(11		MOLE				NA							1		:	
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15	(xi	)	SEQUI	ENCE	DESC	CRIP	rion	:SEQ	ID I	NO:	41:	•				. 1	
,	ATT	GTG	TCG	GTA	ACT	TCA	GGG	GTC	TAC	TCA	GAG	GTT	CAG	CTC	GAG	CAG	48
	Ile	Leu	Sèr	Val	Thr	Ser	Gly	Val	Tyr	Ser	Glu	Val	Gln	Leu	Gln	Gln	
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	TCT	GGG	ACT	GTG	CTG	GCA	ĄGG	CCT	GGG	GCT	TCA	GTG	AAG	ATG	TEC	TGC	96
	ser	GIY	Thr	10	reu	ALA	Arg	Pro	GIY	AĻA	ser	val	rys	Met	ser	ĊĀR	
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	AAG	GCT	TCG	GGC	TAC	ACC	TrirTr	ĂĂC	AGC	TAC	TGG	ATG	CAC	TGG	CTA	AAA	144
25	Lvs	Ala	"Ser	Giv	Tvr	Thr	Phe	Asn	Ser	Tvr	Tro	Met	His	Tro	Val	Lvs	***
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	CAG	AGG	CCT	GGA	CAG	GGT	CTG	GAA	TGG	ATT	GGC	GCG	ATT.	TAT	CCT	GGA.	192
	GIn		Pro	Gly	GIn	Gly	Leu	Glu	Trp	île	Gly	Ala	Ile	Tyr	Pro	Gly	-
30		40					45	•				50					
		2 C M	CAT	A STORE	N.C.C	mac.	ROC	CAC	XXC	mom	ANC	200	200	coc		CTG	240
	yen	VGI	Asp	TIA	Ser	. WALL	SAT	CAG	Agn	Dho	Tare	Agn	Ara	Ala	Tare	LAU	.240
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35	ACT	GÇC	GTC	ACA	TCC	ACC	AGC	ACT	GC.C	TAC	ATG	GAA	CTC	AGA	ACC	Carg	288
•	Thr	Ala	Val	Thr	Ser	Thr	Ser	Thr	Ala	lyr	Met	Glu	Leu	Arg	Ser	Lou	
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40	Thr	ASN	Glu	ASP	ser	ALA	val	JAL.	Pne 95	CAR	TRE	råa	GIU		ıyr	Asp	
40	•			90					33					100	• •		•
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			(B)	T	PE:	nucle	eic a	cid			r	* * * * *		;	. •		
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	(4:)	(D)	STRANDED TOPOLOGY E TYPE:m	:line		le	٠,		·· ·:	•		<u>.</u>	•	•
5	(ii) (iii) (iv)	HYPOTHE ANTISEN	TICAL:no SE:no		•		•	,	:	,	w.	* .		
	(vi)		L SOURCE ORGANISM		е			-		,		. ,	,	んたっ
10	(ix)	FEATURE (A)	: NAME/KEY	:Clone	e 200	3A2				-	Tag 1		: 1	2
	(xi)	• •	E DESCRI				NO:42	2:					:	* . : ""
	ATG GAG	TTC GG	G CTA AA	C TGG	GTT	TTC	CTT	GTA	ACA	CTT	TTA	AAT	GGT	48
15	Mec Glu	Pile GI	y Leu As -15	u irb	Val		-10				ren	Asn -5	GIĀ	y . ·
15	ATC CAG	TGT GA	G GTG AA	G CTG	GTG							•	CAG	96
•	Ile Gin	Cys Gl	u Val Ly	s Leu	Val 5	Glu	Ser	Gl.y	Gly	Gly 10	Leu	Val	Gln	:
20.			T CTC AG											. 144
	15	1 × 23 × 74.	r Leu Ar	20		•		ه مخي	25	- ·-		··· k · · ·		, k *
ı	ACT GAT	TAC TA	C ATG AA	C TGG	GTC Val	CGC	CAG	CCT	CCA.	GGA	. AAG	GAA	CTT	192
25	30 %		35	T. 755.		-,, 3	: <b>8</b> 776	40	.5. <b>20</b> .	, <b>O</b> . , <b>y</b>		21.	45	***
			r TTT AT											.,240
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30			r gtg aa											288
	Tyr Ser	Ala Se 65	r Val Ly	s Gly	Arg	Phe 70	Thr	Ile	Ser	Arg	Asp 75	Asn	Pro	142
			C TAT CT											336
<b>35</b>			u Tyr Le		दिस					727				
Ç.	GCC ACT	TAT TA	C TGT GC	AAGA	GAT	AGG	GGG	GGG	AGG	GAC	TGG	TAC	TTC	384
	95		r Cys Ala	100	3.5			, T. T.	105		ពីលិ≊ី ប	-1-	·	- Y
40			C GCA GG										ACG	,432
	Asp Val	Trp Gl	y Ala Gly 11	Y Thr	Thr	Val	Thr	Val: 120	Ser	Ser	Ala	Lys	Thr 125	Parties in Language St. Language Co.
و نور	ACA CCC								** *	-9/	•2	j. i		.438
45	Thr Pro									M.	141	1 4 4		7. G
	(2) IN	FORMATI	ON FOR SI	EQ ID	NO:	43:								
50	(i)		E CHARAC' LENGTH: 4				٠		di n	· : - : : : : : : : : : : : : : : : : :	## -	1141 · 1	•	•
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5	(ii) (iii (iv) (vi)	)	MOLEO HYPO' ANTI: ORIG: (A	PHET: SENS! INAL	ICAL E:no	no RCE:			į	A.							
10	(ix)		FEAT (A SEQUI	) ENCE	AME/I DESC	CRIP'	rion	:SEQ	ID I				•	g •			
; ·	CTT :( Leu <sub>1</sub> ) -10	gTA Val	ACA	CGT	TTA Leu	AAT Asn -5	GGT Gly	ATC Ile	CAG Gin	TGT Cýs	GAG Glu 1	GTG Val	AAG Lys	CTG Leu	GTG Val 5	GAG Glu	<sup>1</sup> 48
15	TCT:	GGA Gly	GGA Gly	GGC Gly 10	TTG Leu	GTA Val	CAG Gln	CCT Pro	GGG Gly 15	GGT Gly	TCT Ser	CTG Leu	AGA	CTC Leu 20	TCC Ser	TGT Cys	96
: 20	GCA 1	ACT Th <i>r</i>	TCT Ser 25	GGG GGG	TTC Phe	ACC	TTC Phe	ACT Thr 30	GAT Asp	TAC Tyr	TAC Tyr	ATG Met	AAC Asn 35	TGG Trp	GTC Val	CGC	-144
	CAG (C	CCT Pro 40	.CCA Pro	GGA Gly	NAG Lys	GCA :Ala	CTT Leu 45	GAG Glu	TGG	TTG Léu	GGT Gly	TTT Phe 50	ATT	AGA Arg	AAC .Asti	AAA Lys	192
<b>25</b>	GCT Ala	AAT Asn	TAT	TAC Tyr	ACA Thr	ACA Thr 60	GAG :Glu	TAC	AGT Ser	GCA Ala	TCT Ser 65	GTG Val	AAG Lys	GGT Gly	CGG Arg	TTC Phe 70	240
3 <i>0</i>	ACC // Thr		Ser		Asp												
	ACC (Thr I	CTG Leu	AGA Arg	GCT Ala 90	GAG Glu	GAC Asp	AGT Ser	GCC Ala	ACT Thr 95	TAT Tyr	TAC Tyr	TGT Cys	GCA Ala	AGA Arg 100	Asp	Gly GGG	336
35									Val	Trp		Ala		Thr		GTC Val	
40	ACC C	GTC Val 120	TCC Ser	TCA Ser	GCC Ala	AAA Lys	ACG Thr 125	ACA Thr	CCC	3 5 c 1 2 5 c 2 5 c 4	67 6 334 534 3	11 4 15 1 7 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	3 : 31 1		.)	·	411
	(2)	INI	FORM	ATION	FOF	R SE(	] ID	NO:	44:			2.4 ° 2°			26.5 15.7 25.8		
<b>45</b>	(i)		(C)	LE TY ST	ENGTH (PE:1 (RANI ()POLO	1:354 nucle DEDNI DGY:1	l bas eic a ESS: d linea	se pa acid loub]	airs le <sup>™</sup> e	·					71. J Z. Z.2. 4 Al		
50 <sub>°,</sub>	(ii) (iii) (iv) (vi)	) I	ANTIS DRIGI	THET I	CAL: : no SOUF	no RCE:	1.24.		1 . T 0 . F	7,	65 x	JC. re,	.A.*	, ;	de.		s Sag

	(ix)	FEATURE (A)		EY:Clone	e 3KE	311				8			,	
5	(xi)	SEQUENC	E DESC	RIPTION	SEQ	ID I	NO:4	4:			/ /		•	
10	GAC ATT	GTG CT Val Le	G ACA C u Thr C 5	CAG TCT	CCT Pro	GCT Ala	TCC Ser 10	Leu	GCT Ala	GTA Val	Ser	CCT Pro	Leu	·· '48
	GGG CAG	SAGG GC Arg Al 20	C ACC A a Thr I	ATC TCA le Ser	TAC	AGG Arg 25	GCC Ala	AGC Ser	AAA Lys	AGT Ser	GTG Val 30	CAG Gln	TTA Leu	96
15	His; Leu	GOCT AT Ala <sub>L</sub> II 35	e <sub>E</sub> val 1	Tyr Met	His 40	Trp	~Asn	Gln	Gľn	Lys 45	Pro	Gly	Gl'n	i T
20	Pro Pro	AGA :CT	C (CTC (A 1 -Leu ::I 70	TC TAT le Tyr 55	CTT Leu	GTA Val	.TCC :Ser	AAC Asn	CTA Leu 60	GAA GEu	TCT Ser	GGG,	GTC Val	192 L⊥ <i>k</i>
	CCT GCC Pro Ala 65	AGG TTO	e ¿Ser ¿G	GC AGT ly Ser 0	GGG Gly	TCT Ser	:GGG :Gly	ACA Thr 7.5	GAC :	TTC Phe	ACC	.CTC Leu	AAC Asn 80	240
<b>25</b>	ATC CAT	PECT GTO Pro Va	G GAG G L Glu G 85	AG GAG	GAT ) Asp	GCT Ala	GCA Ala 90	ACC .	TAT TYT	TAC Tyr	TGT Cys	CAG Gln 95	CAC His	1. <b>288</b> 55. 7.
<b>30</b>	ATT AGG	Vai Ala	ı Tyr T	CG TTC	GGA Gly	Gly .	GGG .Gly	ACC Thr	AAG Lys	Leu	GAA Glu 110	ATA Fle	AAA Lys	31 <b>336</b>
	CGG ;;GCT Arg ;;Ala	GAT GC: Asp Ale	a Ala P	CA JAT	ren Total	PDA LLT En	00. Al ' ·	20 Sec	නම් ම	5 f. 1 510 :	700 614 00	ru Ciru	i II	
<b>35</b>		FORMATIC SEOUENCI	N <sub>v</sub> POR	SEQ ID	NO: 3									
<b>40</b>		(A) 1 (B) 5 (C) 5	LENGTH: TYPE: nu STANDED TOPOLOG	438 bas cleic a NESS:do Y:linea	e par cid o uble	92₹ '		5. : 1		::		.' ' • ‡	7	
<b>45</b>	(iii) (iv) (vi)	HYPOTHE: ANTISENS ORIGINAL	TICAL:n EE:no L SOURC ORGANIS	10			25 1: G 38:	31 . 2 2	70A		· ( )	ů.		` (
		(A) i SEQUENCI	IAME/KE DESCR	Y:Clone IPTION:	17K	B1 .	d 12 12	∙ 803.	120: - 10 -	LAFT.	, Ž	er, Erek		
50	CTA TGG Leu Trp	GTA CTO Val Leu	ı Leu L	TC TGG eu Trp	Val 1	CCA Pro -5	GGT Gly	TCC	ACT Thr	GGT <sub>1</sub>	GAC Asp	ATT	GTG <u>:</u> Val	48

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5	CTG Leu	ACA Thr 5	CAG Gln	TCT	CCT	GCT Ala	TCC Ser 10	TTA Leu	GCT. Ala	GTA Val	TCT Ser	CTG Leu 15	GGG Gly	CAG Gln	AGG Arg	GCC Ala	96
	TCC Ser 20	ATC 11e	Ser	TAC	AGG Arg	GCC Ala 25	AGC Ser	AAA Lys	AGT Ser	GTC Val	AGT Ser 30	ACA Thr	TCT Ser	GGC	TAT Tyr	AGT Ser 35	144
10	TAT Tyr	ATG Met	His	TGG Trp	AAC Asn 40	CAA Gln	CAG Gin	AAA Lys	CCA Pro	GGA Gly 45	CAG Gln	CCA	CCC Pro	AGA Arg	CTC Leu 50	CTC Leu	192
15	ATC	TAT	Leu	GTA Val 55	TCC Ser	AAC Asn	CTA Leu	GAA Glu	TCT Ser 60	GGG G1 y	GTC Val	CCT Pro	GCC Ala	AGG Arg 65	TTC Phe	AGT Ser	240
	GGC	AGT Ser	GGG Gly 70	TCT Ser	GGG Gly	ACA Thr	GAC Asp	TTC Phe 75	Thr	CTC Leu	AAC Asn	ATC Ile	CAT His 80	CCT Pro	GTG Val	GAG Glu	, 288
<b>20</b>	GAG Glu	GAG Glu 85	GAT Asp	GCT Ala	GCA Ala	ACC Thr	TAT Tyr 90	TAC Tyr	TGT Cys	CAG Gln	CAC His	ATT 11e 95	AGG Arg	GGA Gly	GCT Ála	TAC Tyr	336
25	ACG Thr 100	TTC Phe	GGA Gly	GGG Gly	GGG Gly	ACC Thr 105	AAG Lys	Leu	GAA Glu	Ile	AAA Lys 110	.CGG Arg	GCT Ala	GAT Asp	GCT Ala	GCA Ala 115	394
<b>30</b>	CCA Pro	ACT Thr	GTA Val	TCC Ser	ATC Ile 120	TTC Phe	CCA Pro	CCA Pro	TCC Ser	AGT Ser 125	AAG	CTT Leu	GJA GGG	AAA Lys	CGG Arg 130	TTC Phe	432
		CCG Pro					٠			76	•		* ( )		No.		438 . ·
35	(2) (i)		FORMA SEQUE	ENCE	CHAR	LACTE	RIST	:CS:	نى دىمى		20 C		17.113	Τ (			
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45	(iii) (iv) (vi)	) <i>P</i>	HYPOT ANTIS ORIGI (A) FEATU	ENSE NAL OR	: no SOUR	CE:	ouse		,		2 3 4	e a <sup>fi</sup> ta ar V					• .
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	Leu	Tnr	GIN 5	ser	Pro	Ala	ser	Leu	10	Val	Sr	Leu	GIÀ	Gln 15	Arg		-
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	Thr	Ile	Ser 20	Tyr	Arg	Ala	Ser	Lýs 25	Ser	Val	Ser	Thr	Ser 30	Gly	Tyr	Ser	
	- TAT	ATG	CAC	TGG	AAC	CAA	CAG	AGA	CCA	GGA	CAG	CCA	CCC	AGA	CTC	CTC	240
	Tyr	Met 35	His	Trp	Asn	GIn	40	Arg	Pro	GIĀ	Gln	Pro 45	Pro	Arg	Leu	Leu	
					TCC												288
	11e 50	Tyr	Leu	Val	Ser	Asn 55	Leu	Asp	Ser	Gly	Val 60	Pro	Ala	_	Phe	Ser 65	
	GGC	AGT	GGG	TCT	GGG	ACA	GAC	<b>TTC</b>	ACC	CTC	AAC	ATC	CÁT	CCT	GTG	GAG	336
	Gly	Ser	Glŷ	Ser	Gly 70	Thr	Asp	Phe	Thr	Leu 75	Asņ	Ile	His	Pro	Val 80	Glu	•
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	Glu	Glu	Asp	A1a 85	Ala	Thr	Tyr	Tyr	Cys 90	Gln	His	Ile	Glu	Gly 95	Ala	Tyr	
	ACG	TTC	GGA	GGĜ	GGG Gly	ACC	AAG	CTG	GAA	ATA	AAA			); ` :		ر د د د	417
•	Thr	Phe	Gly 100	Glý	Gly	Thr	Lys	Leu 105	Glu	Ile	ĽÝS	-	23				
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5	GTG Val	ATG Met	ACC Thr 5	CAG Gln	TCT Ser	-CAC His	AAA Lys	TTC Phe 10	ATG Met	TCC Ser	ACA Thr	TCA Ser	GTA Val 15	GGA Gly	GAC Asp	AGG Arg	144
	GTC Val	AGT Ser 20	ATC	ACC Thr	TGC Cys	,AAG Lys	GCC Ala 25	AGT Ser	CAG Gln	GAT Asp	GTG Val	AAT Asn 30	ACT	GCT Ala	GTA Val	GCC Ala	<u>1</u> 92
10	TGG Trp 35	TAȚ T <u>y</u> r	"CAA "Gln	CAG ,Gln	AAA Lys	CCA Pro 40	GGA Gly	CAA Gln	TCT Ser	CCT Pro	AAA Lys 45	CTA Leu	CTG Leu	CTT Leu	TAC Tyr	TCG Ser 50	240
15	GCA Ala	TCC Ser	TAC Tyr	Arg	TAC Tyr 55	ACT Thr	GGA Gly	GTC Val	CÇT Pro	GAT Asp 60	CAC His	TTC Phe	ACT Thr	Gly	AGT Ser 65	GGA .	288
	ŢĊŢ Ser	GGG Gly	ACG Thr	GAT Asp 70	TTC Phe	ACT Thr	TTC Phe	ACC Thr	ATC Ile 75	AGC Ser	GGT G1y	GTG Val	CAG Gln	GCT Ala 80	GAA Glu	GAC Asp	336
20	CTG Leu	GCA Ala	GTT Val 85	TAT Tyr	TAC Tyr	TGT Cys	CAG Gln	CAA Gln 90	CAT His	TAT Tyr	AGT Ser	CCT Pro	CCT Pro 95	CTC Leu	ACG Thr	TTC Phe	384
25						CTG Leu											420
:.	(2)					R SEQ				······································	* ** ; ;	•	-4 \$		ĭ	Section 2	
30	(i)	;	SEQUI (A) (B) (C)	Li Ty	ENGTI (PE : 1 [RANI	RACTE 1:360 nucle DEDNE DGY:1	) bas eic a ESS:s	se pa acid sing]	irs			ī	· }				
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40	(ix)		(A) FEATU (A) SEQUI	JRE:	ME/I	ISM: KEY: ( CRIP)	llone	= ≥ 231	CA26 ID N	٠, ٠		: /: #.	3				
45						ATT Ile	<b>va</b> I'	Met		CAG	Ser		AAA Lys				48
45						AGG Arg			Ile 20	Thr	Cys	Lys					96
<b>50</b>						GCC Ala	Trp	Tyr	CAA	Gln	AAA Lys	Pro	Arg				144
55						-				T							

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AAA CTA CTG ATT TAC TCG GCA TCC TAT CGG TAC ACT GGA GTC CCT GAT 192 Lys Leu Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp CGC TTC ACT GGC AGT GGA TCT GGG ACG GAT TTC ACT TTC ACC ATC AGC 240 Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Ph Thr Phe Thr Ile Ser AGT GTG CAG GCT GAA GAC CTG GCA GTT TAT TAC TGT CAG CAA CAT TAT 10 Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr AGT ACT GCG TGG ACG TTG GGT GGT GGC ACC AAG CTG GAA ATC AAA CCCG 336 Ser Thr Ala Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg 15 GCT GAT GCT GCA CGA ACT GTA TCC Ala ASp Ala Ala Pro Thr Val Ser 110 CONTRACTOR CONTRACTOR SET OF THE THE LATE OF SITE AS TO WELL ం ఉందా కాక్ష్మ్ కాక్ క్షాంత్ . **ైంద**ి region of the experience of th IN THE ROLL OF RESIDENCE AND THE ROLL OF ROLL OF THE Claims 1. An immunoglobulin H chain variable region fragment which contains a hypervariable region CDR1 having an amino acid sequence selected from (1) Ser Tyr Trp Met His; A FOAL A STORY 30 Asp Tyr Tyr Met Asp; and Asn Tyr Trp Met Ging 7001070 a hypervariable region CDR2 having an amino acid sequence selected from consultable and sequence selected from consultable con 35 HEROTA OF LETTER C n inti ..⇒D£O∈... (2) Ala Ile Tyr Pro Gly Asn Ser : ISPUGAL: Asp Ile Ser Tyr Ser Gin Asn 40 Phe Lys Asp; COT DIA 177 ART Phe Ile Arg Asn Lys Alar CDA HOLDER DEL TO Asn Leu Tyr Thr Thr Asp 45 The Day is the Tyra Ser Ala Ser Valo Lysuk has see in any to in the seas a foly; errorer ex the contract that the contract services Phe Ile Arg Asn Lys Ala 50 Asn Tyr Tyr Thr Thr-Glu A 6 a Li Tyr Ser Ala Ser Val Lys Gly; and Ala Ile Tyr Pro Gly Asp 55 Gly Asp Thr Arg Tyr Thr

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Gln Lys Phe Lys Gly

### EP 0 702 082 A1

and a hypervariable region CD has naving an amino acid sequence selected from

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(3) Glu Glu Tyr Asp Týr Asp
Thr Leu Asp Tyr;
Asp Arg Gly Gly Arg Asp
Trp Tyr Phe Asp Val;
Asp Gly Phe Leu Arg Asp
Trp Tyr Phe Asp Val; and
Ser Gly Tyr Tyr Gly Ser
Phe Val Gly Phe Ala Tyr.

# 2. An immunoglobulin H chain variable region fragment having the following amino acid sequence

Glu Val Gln Leu Gln Gln Ser Gly Thr Val
Leu Ala Arg Pro Gly Ala Ser Val Lys Met
Ser Cys Lys Ala Ser Gly Tyr Thr Phe Asn
Ser Tyr Trp Met His Trp Val Lys Gln Arg
Pro Gly Gln Gly Leu Glu Trp Ile Gly Ala
Ile Tyr Pro Gly Asn Ser Asp Ile Ser Tyr
Ser Gln Asn Phe Lys Asp Arg Ala Lys Leu
Thr Ala Val Thr Ser Thr Ser Thr Ala Tyr
Met Glu Leu Arg Ser Leu Thr Asn Glu Asp
Ser Ala Val Tyr Phe Cys Thr Lys Glu Glu
Tyr Asp Tyr Asp Thr Leu Asp Tyr Trp Gly
Gln Gly Thr Ser Val Thr Val Ser Ser

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### EP 0 702 082-A1

### 3. An immunoglobulin H chain variable region fragment having the following amino acid sequence

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Phe Thr Phe Thr Asp Tyr Tyr Met Asn Trp Val Arg Gln Pro Pro Gly Lys Ala Leu Glu Trp Leu Gly Phe Ile Arg Asn Lys Ala Asn Tyr Tyr Thr Thr Glu Tyr Ser Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Ary Asp Asn Ser Gln Ser Ile Leu Tyr Leu Gln Met Asn Thr Leu Arg Ala Glu Asp Ser Ala Thr Tyr Tyr Cys Ala Arg Asp Gly Phe Leu Arg Asp Trp Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val and the Ser Ser. T. L V .5 ÷ , :3,

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## 5 4. An immunoglobulin H chain variable region fragment having the following amino acid sequence

W.

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Ary Leu Ser Cys Ala Thr Ser Gly Leu Thr Phe Thr Asp Tyr Tyr Met Asn Trp Val Arg Gln Pro Pro Gly Lys Glu Leu Glu Trp Leu Gly Phe Ile Arg Asn Lys Ala Asn Leu Tyr Thr Thr Asp Tyr Ser Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Pro Gln Ser Ile Leu Tyr Leu Gln Met Asn Thr Leu Thr Thr Glu Asp Ser Ala Thr Tyr Tyr Cys Ala Arg Asp Arg Gly Gly Arg Asp Trp Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser.

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#### EP.0 702 082 A1

5. An immunoglobulin H chain variable region fragment having the following an in acid sequence

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Glu Val Gln Leu Gln Gln Ser Gly: Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Asn Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Trp Met Gln Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asp Gly Asp Thr Arg Tyr Thr Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Ala Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Ser Gly Tyr Tyr Gly Ser Phe Val Gly Phe Ala Tyr Troogly Gln Gly Thr Leu Val Thr Val Ser 11. The second second second JE ....

DNA and RNA fragments each encoding an immunoglobulin H chain variable region fragment which contains a base sequence encoding a hypervariable region CDR1 having an amino acid sequence selected from ఇం కా కాండ్ల్లో అడి కాండ్ కింద్రం చేస్

受権 加工 更終的 は 1990 日都の

建装 法使担付股票 (第二) 一点

TWO > (1) Servityr Trp Met His; Asp Tyr Tyr Met Ash; and 180 100 L Ash. Tyr Trp Met Gln . 10 1 THE REPORT OF STREET OF THE PARTY OF THE PAR

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a base sequence encoding a hypervariable region CDR2 having an amino acid sequence selected from

WE ON THE TON CAR DATE AT YOUR Ala Ile Tyr Pro Gly Asn Ser Asp Ile Ser Tyr Ser Gln Asn Phe Lys Asp; Phe Ile Arg Asn Lys Ala . Asn Leu Tyr Thr Thr Asp Tyr Ser Ala Ser Val Lys Gly; Phe Ile Arg Asn Lys Ala Asn Tyr Tyr Thr Thr Glu Tyr Ser Ala Ser Val Lys Gly; and Ala Ile Tyr Pro Gly Asp Gly Asp Thr Arg Tyr Thr

Glu Lys Phe Lys Gly .

#### EP 0 702 082 A1

a base sequence encoding a hypervariable region CDR3 having an amino acid sequence selected from

,	Glu	Glu	Tyr	Asp	Tyr	Asp
	Thr	Leu	Asp	Tyr	<u>;</u>	•
	Asp	Arg	Gly	Gly	Arg	Asp
	Trp	Tyr	Phe	Asp	Val	;
	Asp	Gly	Phe	Leu	Arg	Asp
٠	Trp	Tyr	Phe	Asp	Val	, and
	Śer	Gly	Tyr	Tyr	Gly	Ser
	Phe	Val	Gly	Phe	Ala	Tyr
	39 3	1. 19			٠ ,	±\

7. An immunoglobulin H chain variable region fragment having following base sequence:

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GAG GTT CAG CTC CAG CAG TCT GGG ACT GTG
CTG GCA AGG CCT GGG GCT TCA GTG AAG ATG
TCC TGC AAG GCT TCG GGC TAC ACC TTT AAC
AGC TAC TGG ATG CAC TGG GTA AAA CAG AGG
CCT GGA CAG GGT CTG GAA TGG ATT GGC GCG
ATT TAT CCT GGA AAT AGT GAT ATT AGC TAC
AGC CAG AAC TTT AAG GAC AGG GCC AAA CTG
ACT GCC GTC ACA TCC ACC AGC ACT GCC TAC
ATG GAA CTC AGA AGC CTG ACA AAT GAG GAC
TCT GCG GTC TAT TTC TGT ACA AAA GAG GAA
TAT GAT TAC GAC ACC CTG GAC TAC TCG GGT
CAA GGA ACC TCA GTC ACC GTC TCC TCA.

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# 8. An immunoglobulin H chain variable region fragment having the following base sequence.

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GAG GTG AAG CTG GTG GAG TCT GGA GGA GGC
TTG GTA CAG CCT GGG GGT TCT CTC AGA CTC
TCC TGT GCA ACT TCT GGG TTA ACC TTC ACT
GAT TAC TAC ATG AAC TGG GTC CGC CAG CCT
CCA GGA AAG GAA CTT GAA TGG TTG GGT TTT
ATT AGA AAC AAA GCT AAT CTT TAC ACA ACA
GAC TAC AGT GCA TCT GTG AAG GGT CGG TTC
ACC ATC TCC AGA GAT AAT CCC CAA AGC ATC
CTC TAT CTT CAA ATG AAC ACC CTG ACA ACT
GAG GAC AGT GCC ACT TAT TAC TGT GCA AGA
GAT AGG GGG GGG AGG GAC TGG TAC TTC GAT
GTC TGG GGC GCA GGG ACC ACG GTC ACC GTC

### 25 9. An immunoglobulin-H chain variable region fragment having the following base sequence

GAG GTG AAG CTG GTG GAG TCT GGA GGA GGC

TTG GTA CAG CCT GGG GGT TCT CTG AGA CTC

TCC TGT GCA ACT TCT GGG TTC ACC TTC ACT

GAT TAC TAC ATG AAC TGG GTC CGC CAG CCT

CCA GGA AAG GCA CTT GAG TGG TTG GGT TTT

ATT AGA AAC AAA GCT AAT TAT TAC ACA ACA

GAG TAC AGT GCA TCT GTG AAG GGT CGG TTC

ACC ATC TCC AGA GAT AAT TCC CAA AGC ATC

CTC TAT CTT CAA ATG AAC ACC CTG AGA GCT

GAG GAC AGT GCC ACT TAT TAC TGT GCA AGA

GAT GGG TTC CTA CGG GAC TGG TAC TTC GAT

GTC TGG GGC GCA GGG ACC ACG GTC ACC GTC

TCC TCA.

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10. An immunoglobulin H chain variable region fragment having the following base sequence

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GAG GTT CAG CTC CAG CAG TCT GGG GCT GAA

CTG GCA AGA CCT GGG GCT TCA GTG AAC TTG

TCC TGC AAG GCT TCT GGC TAC ACC TTT ACT

AAC TAC TGG ATG CAG TGG GTA AAA CAG AGG

CCT GGA CAG GGT CTG GAA TGG ATT GGG GCT

ATT TAT CCT GGA GAT GGT GAT ACT AGG TAC

ACT CAG AAG TTC AAG GGC AAG GCC ACA TTG

ACT GCA GCT AAA TCC TCC AGC ACA GCC TAC

ATG CAA CTC AGC AGC TTG GCA TCT GAG GAC

TCT GCG GTC TAT TAC TGT GCA AGA TCG GGC

TAC TAT GGT AGC TCC GTT GGG TTT GCT TAC

TGG GGC CAA GGG ACT CTG GTC ACT GTC TCT

GCA .

25 11. An immunoglobulin L chain variable region fragment which contaîns a hypervariable region CDR1 having an amino acid sequence selected from

(1) offyr Arg Ala Ser Lys Ser Val

Gin Leu His Leu Alatile Val

Tyr Arg Ala Ser Lys Ser Val

Offyr Arg Ala Ser Lys Ser Val

Off Con Met His Tor Son Tyr

Met His Tor Son Tyr

Lys Ala Ser Gin Asp Val Asn

Lys Ala Ser Gin Asp Val Throm

Thr Asp Val Ala ...

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a hypervariable region CDR2 having an amino acid sequence selected from  $m_{\rm CCT}$ 

(2) Leu Val Ser Asn Leu Glu Ser; Leu Val Ser Asn Leu Asp Ser; and Ser Ala Ser Tyr Arg Tyr Thr.

### EP 0 702 082 A1

## and a hypervariable region CDRs naving an amino acid sequence selected from

(3) Gln His Ile Arg Val Ala Tyr
Thr;
Gln His Ile Arg Gly Ala Tyr
Thr;
Gln His Ile Glu Gly Ala Tyr
Thr;
Gln Gln His Tyr Ser Pro Pro
Leu Thr; and
Gln Gln His Tyr Ser Thr Ala
Trp Thr.

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# 12. An immunoglobulin L chain variable region fragment having the following amino acid sequence

Asp Ile Val Leu Thr Gln Ser Fro Ala Ser
Leu Ala Val Ser Pro Leu Gly Gln Arg Ala
Thr Ile Ser Tyr Arg Ala Ser Lys Ser Val
Gln Leu His Leu Ala Ile Val Tyr Met His
Trp Asn Gin Gln Lys Pro Gly Gln Pro Pro
Arg Leu Leu Ile Tyr Leu Val Ser Asn Leu
Glu Ser Gly Val Pro Ala Arg Phe Ser Gly
Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn
Ile His Pro Val Glu Glu Glu Asp Ala Ala
Thr Tyr Tyr Cys Gln His Ile Arg Val Ala
Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu
Ile Lys

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### 13. An immunoglobulin L chain variable region fragment having the following amino acid sequence "

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Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Ser Ile Ser Tyr Arg Ala Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser Tyr Met His Trp Asn Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr Leu Val Ser Asn Leu Glu Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ile Arg Gly Ala Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys.

### 14. An immunoglobulin la chain variable region fragment laving the following amino acid sequence

医腹腔 医铁铁铁 经通证 医二氯苯二甲基

Asp The Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Tyr Arg Ala Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser Tyr Met His Trp Asn Gln Gln Arg Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr Leu Val Ser Asn Leu Asp Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ile Glu Gly Ala Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys.

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### 15. An immunoglobulin L chain variable region fragment having the following amino acid sequence

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Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Leu Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp His Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Gly Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Pro Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys

# 16. An immunoglobulin L chain variable region fragment having the following amino acid sequence

1 00 % 1 10 May 120 Mg . The

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Thr Thr Asp Val Ala Tro Tyr Gln Gln Lys Pro Arg Gln Ser Pro Lys Leu Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Thr Ala Tro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys

### EP 0 702 082 A1

17. DNA and RNA fragments each encoding an immunoglobulin le chain variable region fragment which contains a base sequence encoding a hypervariable region CDR1 having an amino acid sequence selected from

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Tyr Arg Ala Ser Lys Ser Val
Gln Leu His Leu Ala Ile Val
Tyr Met His;
Tyr Arg Ala Ser Lys Ser Val
Ser Thr Ser Gly Tyr Ser Tyr
Met His;
Lys Ala Ser Gln Asp Val Asn
Thr Ala Val Ala; and
Lys Ala Ser Gln Asp Val Thr
Thr Asp Val Ala,

a base sequence encoding a hypervariable region CDR2 having an amino acid sequence selected from

(2) Leu Val Ser Asn Leu Glu Ser;
Leu Val Ser Asn Leu Asp Ser; and

Ser Ala Ser Tyr Arg Tyr Thr;

and a base sequence encoding a hypervariable region CDR3 having an amino acid sequence selected from

Gln His Ile Arg Val Ala Tyr
Thr;
Gln His Ile Arg Gly Ala Tyr
Thr;
Gln His Ile Glu Gly Ala Tyr
Thr;
Gln Gln His Tyr Ser Pro Pro
Leu Thr; and
Gln Gln His Tyr Ser Thr Ala
Trp Thr.

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cc

### EP 0 702 032 A1

# 18. An immunoglobulin L chain variable region fragment having the foll wing base sequence

**5** 

GAC	TTA	GTG	CTG	ACA	CAG	TCT	CCT	GCT	TCC
TTA	GCT	GTA	TCT	CCT	CTG	GGG	CAG	AGG	GCC
ACC	ATC	TCA	TAC	AGG	GCC	AGC	AAA	AGT	GTG
CAG	TTA	CAT	CTG	GCT	ATA	GTT	TAT	ATG.	CAC
TGG	AAC	CAA	CAG	AAA	CCA	GGA	CAG	CCA	CCC
AĢA	CTC	$C\bar{T}C$	AT <sub>i</sub> C	TAT	CTT	GTA	TCC.	AAC	CTA
GAA	TCT	GGG	GTC	CCT	GCC	AGG	TTC	AGT	GGC
AGT	GGG	TCT	GGG	ACA	GAC	TTC	ACC	CTC	AAC
ATC	CAT	CCT	GTG	GAG	GAG	GAG	GAT '	GCT	GCA
ACC	TAT	TAC	TGT	CAG	CAC	ATT	AGG	GTA:	GCT
TAC	ACG	TTC	GGA	GCG	GGG	ACC	AAG	CIG	GAA
ATA	AAA	•					•		

# 19. An immunoglobulin L chain variable region fragment having the following base sequence

								-		
GAC	ATT	GTG	CTG	ACA	CAG	TCT	CCT	GCT	TCC	
TTA	GCT	GTA	TCT	ÇŢĞ	GGG	CAG	AGG	GCC	TCC	
ATC	TCA	TAÇ	AGG	GCC	AGC	ÁAA	AGT	GTC	AGT	
ACA	TCT	GÇÇ	TAT	AGT	TAT	ATG	CAC	TGG	AAC	
CAA	CAG	AAA	CCA	GGA	CAG	CCA	CCC	AGA	CTC	
CTC	ATC	TAT	CLL	GTA	ŢÇÇ	AAC	CTA	GAA	TCT	
ĢĢĞ	GTC	CCT	GCC	AGG	TTC	AGT	ĢGC	AGT	GGG	
** ***	GGG	ACA	GAÇ	TTC	ACC	CTC	AAC	ATC	CAT	
CCT	GŢĢ	GAG	GAG	GAG		GCT	GCA	ACC		
TAC	TĞT	ĆĀĠ		ATT	AGG	GGA	GCT	TAC	ACG	
TTC	GGA	GGG	GGG	ACC		CTG	GAA	ATA	AAA	

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### EP 0 702 082 A1

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### 20. An immunoglobulin L cham variable region fragment having the following base sequence

GAC ATT GTG CTG ACA CAG TCT CCT GCT TCC
TTA GCT GTA TCT CTG GGG CAG AGG GCC AGC
ATC TCA TAC AGG GCC AGC AAA AGT GTC AGT
ACA TCT GGC TAT AGT TAT ATG CAC TGG AAC
CAA CAG AGA CCA GGA CAG CCA CCC AGA CTC
CTC ATC TAT CTT GTA TCC AAC CTA GAC TCT
GGG GTC CCT GCC AGG TTC AGT GGC AGT GGG
TCT GGG AGA GAC TTC ACC CTC AAC ATC CAT
CCT GTG GAG GAG GAG GAT GCT GCA ACC TAT
TAC TGT CAG CAC ATT GAG GGA GCT TAC ACA
TTC GGG AGG GGG ACC AAG CTG GAA ATA AAA.

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# 21. An immunoglobulin L chain variable region fragment having the following base sequence enterprise Ladin éwone നില്ല വിധാന വേശ്യം ലില്ലാന് പ്രവേശം

GAC ATT GTG ATG ACC CAG TCT CAC AAA TTC ATG TĈC ACA TĈA GTÁ GGA GAC AGG GTC ATC ACC TGC AAG GCC AGT CAG GAT ACT GCT GTA GCC TGG TAT CAA CAG AAA GGA CAA TOT COT AAA CTA CTG CTT TCG GCA TCC TAC CGG TAC ACT GGA GTC CCT CAC TIC ACT GGC AGT GGA TCT GGG ACG TIC ACT TIC ÁČĆ ATC AGC GGT GTG CAG GCT GAA GAC CTG GCA GTT TAT TAC TGT CAG CAA CAT TAT AGT CCT CCT CTC ACG TTC GGT GGG ACC AAG CTG GAA CTG AAA

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# 22. An immunoglobulin L chain variable region fragment having the following base sequence

GAC	ATT	GTG	ATG	ACA	CAG	TCT	CAC	AAA	TTC
ATG	TCC	ACA	TCA	GTT	GGA	GAC	AGG	GTC	ACC
ATC	ACC	TGC	AAG	GCC	AGT	CAG	GAT	GTG	ACT
ACT	GAT	GTA	GCC	TGG	TAT	CAA	CAG	AAA	CCA
CGA	CAA	TCT	CCT	AAA	CTA	CTG	ATT	TAC	TCG
GCA	TCC	TAT	CGG	TAC	ACT	GGA	GTC	CCT	GAT
CGC	TTC	ACT	GGC	AGT	GGA	TCT	GGG	ACG	GAT
TTC	ACT	TTC	ACC	ATC	AGC	AGT	GTG	CAG	GCT
GAA	GAC	CTG	GCA	GTT	TAT	TAC	TGT	CAG	CAA
CAT	TAT	AGT	ACT	GCG	TGG	ACG	TTC	GGT	GGT
GGC	ACC	AAG	CTG	GAA	ATC	AAA	_		

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23. An Fv region fragment comprising the immunoglobulin H chain variable region fragment according to claim 2 and the immunoglobulin L chain variable region fragment according to claim 12.

24. An Fv region fragment comprising the immunoglobulin H chain variable region fragment according to claim 2 and the immunoglobulin L chain variable region fragment according to claim 13.

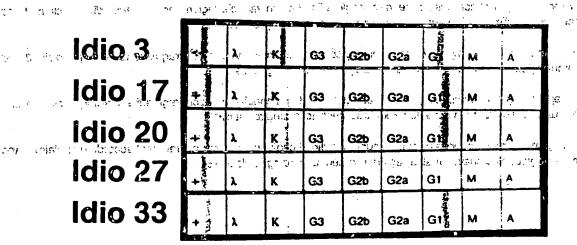
- 25. An Fv region fragment comprising the immunoglobulin H chain variable region fragment according to claim 3 and the immunoglobulin L chain variable region fragment according to claim 14.
- 26. An Fv region fragment comprising the immunoglobulin H chain variable region fragment according to claim 4 and the immunoglobulin L chain variable region fragment according to claim 15.
- 27. An Fv region fragment comprising the immunoglobulin H chain variable region fragment according to claim 5 and the immunoglobulin L chain variable region fragment according to claim 16.

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# FIG. I



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FIG. 2

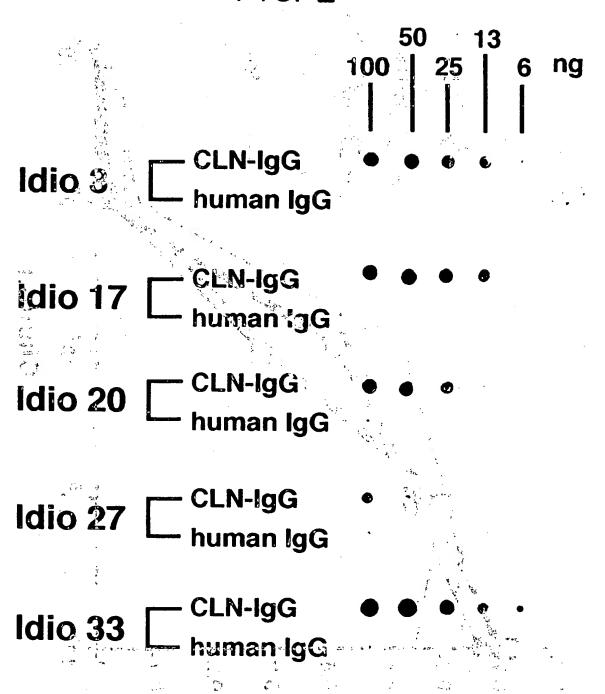
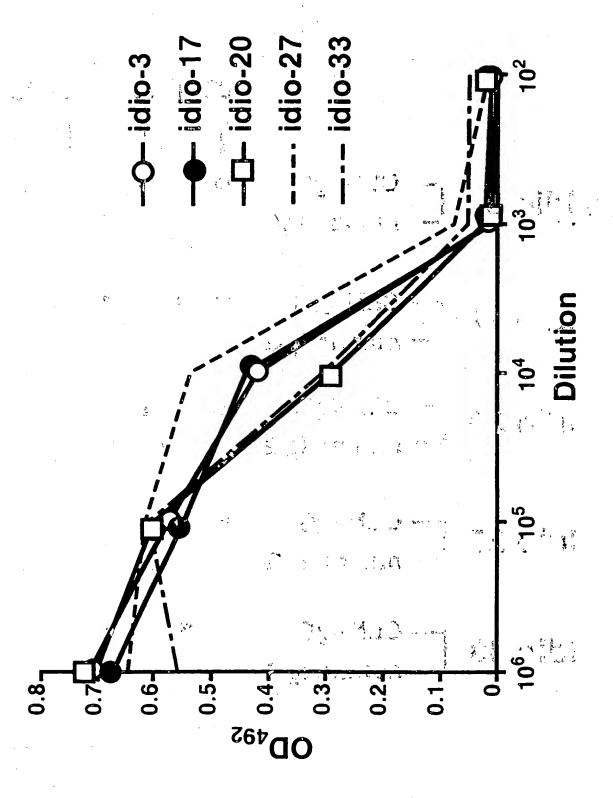


FIG. 3



# FIG. 4

3 17 20 27 33

_ 3	17	20	27	33	
Glu	Glu	Glu	Glu	Glu	1
Val	Val				
		Lys	Lys	Lau	
Gln	Gln	Gly	Glu		
Ser	Ser				1
		GLY	GLY	Gly	1
		Glv	Glv		l
Leu-	Leu	Leu			ĺ
	Ala	· Val			
	Glv	Glv	Glv		
		GLy	Gly		
					1
Cy3	Cys	··Cys	Cys	Cys	
Lys	Lys	Alc	Ala		
	Ser	Ser.	TINE		١.
A	Gly	์ เรา	GIV	Glv	
	Туг	: Leu	∵Phe	Tyr	
			Phe	Phe	
					•
Tyr	Туг	. Tyr	Tyr	Tyr	
Trp	- Trp	. Tyr.	Tyr	∉ Trp	
Met	Met	Met	. Het	z Het	
		· · · -			
					1
	Lvs	" Arc	"Ara		'
Gln	~Gtn_	Gln	"Gln	Gln	
	". C1	V 63 . 1	5 209	Pro	
Glin	Gln	Lvs	Lvs		1
Gly	~,,	9 6 6	~		
Leu				Leu	
	_				· :
Ile	Ile	irp Leu	irp Leu		ì
Gly	Gly	Gly	- Gl.y-	GLY	•
Ala				Ala	
Ile	.Ile Tvr	Ile	Ile	Lle	•
Pro	Pro			Pro	
		Ala	Ala		
ΔSn	ASD	rea	ıyr	ASP	
		Tvr		GIV	
Ser Asp	Ser Asp	Tyr Thr	Tyr	Gly	
Ser Asp Ile	Ser Asp Ile	Thr Thr	Tyr	Gly Asp Thr	
Ser Asp Ile Ser	Ser Asp Ile Ser	Thr Thr Asp	Tyr Thr Thr Glu	Asp Thr Arg	
Ser Asp Ile Ser Tyr	Ser Asp Ile Ser Tyr	Thr Thr Asp Tyr	Tyr Thr Thr Glu Tyr	Asp Thr Arg Tyr	
Ser Asp Ile Ser Tyr Ser	Ser Asp Ile Ser Tyr Ser	Thr Thr Asp Tyr Ser	Tyr Thr Thr Glu Tyr Ser	Asp Thr Arg Tyr Thr	
Ser Asp Ile Ser Tyr	Ser Asp Ile Ser Tyr Ser Gln Asn	Thr Thr Asp Tyr	Tyr Thr Thr Glu Tyr	Asp Thr Arg Tyr	
Ser Asp Ile Ser Tyr Ser Gln Asn Phe	Ser Asp Ile Ser Tyr Ser Gln Asn Phe	Thr Thr Asp Tyr Ser Ala Ser Val	Tyr Thr Thr Glu Tyr Ser Ala Ser Val	Asp Thr Arg Tyr Thr Gln Lys Phe	
Ser Asp Ile Ser Tyr Ser Gln Asn Phe Lys	Ser Asp Ile Ser Tyr Ser Gln Asn Phe Lys	Thr Thr Asp Tyr Ser Ala Ser Val Lys	Tyr Thr Thr Glu Tyr Ser Ala Ser Val Lys	Asp Thr Arg Tyr Thr Gln Lys Phe	
Ser Asp Ile Ser Tyr Ser Gln Asn Phe	Ser Asp Ile Ser Tyr Ser Gln Asn Phe	Thr Thr Asp Tyr Ser Ala Ser Val	Tyr Thr Thr Glu Tyr Ser Ala Ser Val	Asp Thr Arg Tyr Thr Gln Lys Phe	
	Value Glan Ser Gly Thr Value Alas Ser Value Alas Se	Glu Glu Glu Gln	Glu Glu Glu Glu Val Val Val Val Val Gln Gln Gln Gln Gln Gln Gln Gln Gln Gl	Glu Glu Glu Glu Val Val Val Val Gln Gln Gln Lys Lys Leu Leu Leu Leu Gln Gln Gln Glu Glu Ser Ser Ser Ser Gly Gly Gly Gly Thr Thr Gly Gly Val Val Gly Gly Val Val Gly Gly Leu Leu Leu Ala Ala Gly Gly Gly Gly Gly Gly Ala Ala Gly Gly Ser Ser Ser Val Val Leu Leu Lys Lys Arg Arg Met Met Leu Leu Lys Lys Arg Arg Ala Ala Thr, Thr Ser Ser Ser Ser Gly Gly Gly Gly Gly Gly Gly Tyr Tyr Leu Phe Thr Thr Thr Thr Thr Thr Thr Ser Ser Ser Ser Gly Tyr Tyr Tyr Tyr Tyr Tyr Tyr Met Met Met Met Het His His Asn Asn Trp Trp Trp Trp Val Val Val Lys Lys Arg Arg Gln Trp	Glu Glu Glu Glu Glu Val

68	Lys	Lys	Thr	Thr	Th
: 6 <del>9</del> 70	Leu	Leu	Ile	Ile	Le
71	Ala	Thr Ala	Ser	Ser	Th
72	Val	Val	Arg Asp	Arg Asp	Al
73	The	Thr	ASP	ASP	Al- Ly
74	Ser	Ser		Ser	Se
75	Thr	The	Gln	Gln	Se
7€	Ser	Ser	Ser	Ser	Se
. 77,	The	The	Ile	Ile	Th
78	Ala.	:Ala	Leu	Leu	Al
. 79	Tye		Tyr	Tyr	Ty
F 80	Het.		, l·eu	Leu	Жe
£0, 01	Glu	Glu	Gln	a so	GL
	Leu	Leu	Met	Met	Le
3 82A	Arg	::Arg	"Asn	Asn	Se
. 82B,	Ser,		Thr	Thr	Se
82C 83	Leu	·Leu	Leu	Leu	Le
84	Thr		Thr	Arg	Al
85	Asn	Asn		Ala	Se
85	ASP	Asp	;Glu Asp	,Glu Asp	Gl
	Ser	Se:	Ser	Ser	As: Se
. 88	Ala	Ala	Ala	Ala	Al
. 89	Val	Val	Thr	Thr	Va
90	Tyr	Tyr	Tyr	Tyr	Тy
91	Phe	Phe	Tyr	Туг	Тy
. 92	Cys		Cys	Cys	Ċý
93	Thr	Thr	Ala	Ala	Al
94	Lys	Lys.	.Arg	Arg	Ar
95;	Glu	Glv	Asp	Asp	Se
96 ···	Glu	Glu	Arg	Gly	GL
- 97	Tyr	Tyr		Phe	Ty
98	Asp	Asp	Gly	Leu	Ty
	•	• • •			
. 99	Tyr	≀Tyr-	Arg	Arg	Gly
C 160	Asp	Asp	Asp	Asp	Sei
D 1004	Thr	Thr			Pho
P 1003			;		Val
. 4 TOOL			,`		GL
1690					
100E	-474				
100F	:				
100G 103H					-,-
1007					
160)	-5-		Trp	Trap	<u>-</u>
1005		Leu	Tyr Phe	Ty:- Phe	Phe
101	Asp		Asp	Asp	Alc
า∺ે 102	Tyr	Tyr	Val.	Val	Tyr
103	Trp	Tro	Trp	Trp	Tre
2 104	Gly	GUy	Gly	Gly	GL)
105	Gln	Gln	Ala	Ala	Glr
106	Gly	Gly	Gly	Gly	GLY
F 107	Thr	Thr	The"	Thr	Thr
R 108	Ser	Ser	Thr-	Thr	Leu
4 109	Val:	Val	Val	Val	Val
110	Thr	Thr	Thr ]	The	Thr
111	Val	Val		Val	Val
112	Ser	Ser	Ser	Ser	Ser
113	Ser	Ser-	Ser	Ser	Ala

# FIG. 5

		3	17	20	27	33
Γ	1	Asp	Asp	Asp	Asp	Asp
ŀ	2	Ile	Ile	Ile	Ile	Ile
1	. 3	Val		Val	Val	Val   Met
١.	. 4 . 5	Leu Thr	Leu Thr	. Leu. · Thr	· Met Thr	Thr
Ŀ	. 6	Gln		Gln	Gln	Gln
1	. 7	Ser	Ser	Ser	Ser	Ser
	8	Pro	Pro	Pro	His	His
	9	Ala	Ala	Ala:	Lys	Lys
ŀ	. 10	Ser	Ser	Ser	Phe	Phe
1	11	Leu	Leu	Leu	Met	Het
1	F 12	Ala	Ala	Val.	Ser Thr	Ser
ľ	1 14 2	√Val ∴Ser	Val Ser	Şer	Ser	Ser
	15			Leu	Val	Val
ľ	16	Leu		Gly.		Gly
;	: 17 t	Gly	Gln	Gln		Asp
	9 / <b>18</b>	Gln	Arg		Arg	Arg
Ŧ	19		Ala		½ Val	Val
1	20	Ala		Thr	Ser Ile	Thr
1	21 22		Ile Ser	Ser.	Thr	Thr
1	22	Ile Ser	Ser	3er		Cys
┢	24	Tyr	Tyr	Tyr	Lys	Lys
1	25	Arg	Arg	· Arg	Ala	Ala
1	26	Ala	Alo	Ala	Ser	Ser
	<b>27</b> .	Ser	Ser	Ser		Gln
1	278	Lys	Lys	Lys Ser		
.   <u>,</u>	27B :	Val	"Ser Val	Val		
	C 270	Gln				4
	D 27E	Leu	Thr	Thr	t	
4	R 27F	•	6 - ~ <del>;</del> -			1
1	1 28	Leu	Ser	Şer	Asp	Asp
1	29	Ala	Gl·y	Gly:	. Val	Val
٠	. 2. 30 :	Ile	Tyr	. Tyr:		Thr
1	- 31	Vail	Seri	Ser		Thr
	- 32 -		-Tyr		. Ala . Val	Asp Val
۲	33 .		- Met - His			Ala
-	35	Trp	Trp			Trp
-	36 -	Asn	Asn	- Asn.		Tyr
-	. 37	Gln	Gl n.			Gln
1	38 .	Gln	Gln			Gln
-	F : 39		.Lys .Pro	Arg	Lys Pro	Lys Pro
1	H 41.		Gly			Arg
	2 42	Glin	Glm	Glm		Gln
		Pro	Pro	Pro,	: Ser	Ser
-1	44			Pro		Pro
	∴ 45	Ang	Ang	Arg	Lys	Lys Leu
4	46 47	Leu	;:Leu ;:Leu	Leu		Leu
, l'	48	Ile	Ile	Ile		Ile
١,			⇒Tyr_	Tyr	Туг	Tyr
7	50	Leu	Leu	Leu		Ser
	C 51.	Val	Val-	Val	Ala	Ala
.   '	D 53	Ser		Ser Asn		Ser Tyr
.1	R 54	Asn	Asn. Leuج,	Leu		Arg
4	2 .55	Glu			Tyr	Tyr
	56	Ser		Ser		Thr
Γ	57	Gly	Gly			Gly
	58	Val	Val	Val		Val
	59 60	Pro				Pro Asp
	60 61	Ala				Asp
	62	Phe				Phe
	63	Ser	Ser	Ser	Thr	Thr
	64	Gly	Gly	Gly	Gly	Gly

Gly Gly Gly Gly Gly Gly Gr Ser Ser Ser Gly From Phe Phe Phe Phe From Phe Phe Phe From Phe Phe Phe From Phe Phe Phe From Phe Phe From Phe Phe Phe From	65	Ser	Ser	Ser	Ser	Ser
Gly	66		Gly	Gly	Gly	Gly
70 Asp Asp Asp Asp Asp Phe						
Phe Phe Phe Phe Phe 72   Thr	69		Thr		Thr	Thr
Thr Thr Thr Thr Thr Thr Thr Leu Leu Leu Leu Phe Phe Asn Asn Asn Thr Thr Ile		'				
T3    Leu   Leu   Leu   Phe   Phe						
75   Ile   Ile   Ile   Ile   Ile   Ile   His   His   His   Ser   Ser   Fr   Fr   Fr   Fr   Fr   Fr   Fr	- •					Phe
76 His His His Ser Ser Pro Pro Pro Pro Ser Ser Pro Pro Pro Ser Ser Val Val Val Val Val Val Glu Glu Glu Glu Glu Glu Glu Glu Glu Gl						
F 78 Val		TIE	"rre			
F 78 Val Val Val Val Val R 79 Glu Glu Glu Glu Gln Gln Gln Glu	_ 3 77	1				
3 80 Glu Glu Glu Ala Ala 81 Glu Glu Glu Glu Glu 82 Asp Asp Asp Asp Asp 83 Ala Ala Ala Leu Leu 84 Ala Ala Ala Cala Ala 85 Thr Thr Thr Val Val 86 Tyr Tyr Tyr Tyr Tyr 87 Tyr Tyr Tyr Tyr Tyr 88 Cys Cys Cys Cys Cys Cys 89 Gln Gln Gln Gln Gln 91 Ite Ite Ile His His 92 Arg Arg Glu Tyr Tyr 94 Ala Ala Ala Pro Thr 95 Arg Arg Glu Tyr Tyr 958	' <b>F</b> ' 78					
81 Glu Glu Glu Glu 82 Asp Asp Asp Asp Asp 83 Ala Ala Ala Leu Leu 84 Ala Ala Ala Ala Ala Ala 85 The The The Val Val 86 Tyr Tyr Tyr Tyr Tyr 87 Tyr Tyr Tyr Tyr Tyr 88 Cys Cys Cys Cys Cys 89 Gln Gln Gln Gln Gln 90 His His His Gln Gln 91 Ite Ite Ile His His C 92 Arg Arg Gly Gly Ser Ser 95 Ala Ala Ala Pro Thr R 96 Ala Ala Ala Pro Thr R 97 Thr 7 Thr 7 Thr R 10 Ala Ala Ala Pro Thr R 96 Ala Ala Ala Pro Thr R 96 Ala Ala Ala Ala Pro Thr R 96 Ala Ala Ala Ala Pro Thr R 97 Thr 7 Thr 7 Thr 1 Thr R 98 Ala Ala Ala Ala Pro Thr R 97 Thr 7 Thr 1 Thr R 1 Thr 1 Thr 1 Thr						
83 Ala Ala Ala Leu Leu  84 Ala Ala Ala Ala Leu Leu  85 Thr Thr Thr Val Val  86 Tyr Tyr Tyr Tyr Tyr Tyr  87 Tyr Tyr Tyr Tyr Tyr  88 Cys Cys Cys Cys Cys Cys  89 Gin Gin Gin Gin Gin  91 Ite Ite Iie His His  92 Arg Arg Gly Gly Tyr  94 Ala Ala Ala Pro Thr  R 95  950  950  950  950  950  950  950	<b>U</b>	1				
84 Ala Ala Ala Ala Ala BS The The The Val Val Val Tyr	82	1				
85 The The The Val Val 86 Tyr Tyr Tyr Tyr Tyr 87 Tyr Tyr Tyr Tyr Tyr 88 Cys Cys Cys Cys Cys Cys 89 Gln Gln Gln Gln Gln 90 His His His Gln Gln 91 Ite Ite Ile His His C 92 Arg Arg Gla Tyr Tyr Yar Gly Gly Ser Ser Ala Ala Ala Pro Thr R 95 Ala Ala Ala Ala Pro Thr R 95 Ala Ala Ala Pro Thr R 95 Ala Ala Ala Ala Pro Thr R 95 Ala						
86 Tyr Tyr Tyr Tyr Tyr 87 Tyr Tyr Tyr Tyr Tyr 88 Cys Cys Cys Cys Cys Cys Cys 89 Gln Gln Gln Gln Gln 90 His His His Gln Gln 91 Ite Ite Ile His His C 92 Arg Arg Gla Tyr Tyr Yal' Gly Gly Ser Ser D 94 Ala Ala Ala Pro Thr R 95 Ala Ala Ala Ala Pro Thr R 95 Ala Ala Ala Ala Pro Thr R 95 Ala Ala Ala Ala					Val	
88 Cys Cys Cys Cys Cys  89 Gin Gin Gin Gin  90 His His His Gin Gin  91 Ite Ite Ite His His  C 92 Arg Arg Gla Tyr Tyr  yal Gly Gly Ser Ser  R 95 Ala Ala Ala Pro Thr  R 95 Ala Ala Ala Pro Thr  8 95 Ala Ala Ala Pro Thr  9 95 Ala Ala Ala Ala Pro Thr  9 95 Ala Ala Ala Pro Thr  9 95 Ala Ala Ala Pro Thr  9 9 9					Tyr	Tyr
89 Gln Gln Gln Gln Gln 90 His His His Gln Gln 91 Ite Ite Ite His His Gln 91 Te Ite Ite His His Gln 91 Gly Gly Gly Ser Ser 93 Yaf Gly Gly Ser Ser 950						CVS
91 Ite Ite Ite His His C 92 Arg Arg Gla Tyr Tyr yal Gly Gly Ser Ser P 94 Ala Ala Ala Pro Thr R 95						
C 92 Arg Arg Gla Tyr Tyr ydl Gly Gly Ser Ser Ala Ala Ala Pro Thr Pro Ala 3 95A						
D 94 Ala Ala Ala Pro Thr R 95		1	Are	Gla	HIS	
958	V. 03				Ser	
950 950 956 96 Tyr Tyr Tyr Leu Trp 97 Thr Thr Thr Thr 98 Phe Phe Phe Phe 99 Gly Gly Gly Gly Gly F 100 Gly Gly Gly Gly Gly F 101 Gly Gly Gly Gly Gly P 102 Thr Thr Thr Thr Thr A 103 Lys Lys Lys Lys 105 Glu Glu Glu Glu Glu 106 Ile Ile Ile Leu Ile						
958 950 951 952 96 Tyr Tyr Tyr Leu Trp 96 Tyr Tyr Tyr Leu Trp 97 Thr Thr Thr Thr 102 Gly Gly Gly Gly Gly Gly 102 Gly Gly Gly Gly Gly Gly 103 Gly Gly Gly Gly Gly Gly 104 Leu Leu Leu Leu Leu 105 Glu Glu Glu Glu Glu 106 Ile Ile Ile Leu Ile						
950 950 956 1 yr Tyr Tyr Leu Trp 1 yr Thr Thr Thr Thr 98 Phe Phe Phe Phe Phe 99 Gly Gly Gly Gly Gly Gly F 100 Gly Gly Gly Gly Gly Gly R 102 Thr Thr Thr Thr Thr 4 103 Lys Lys Lys Lys 106 Glu Glu Glu Glu Glu 105 Glu Glu Glu Glu Glu 106 Ile Ile Ile Leu Ile 1060		L				
96 Tyr Tyr Tyr Leu Trp 96 Tyr Tyr Tyr Leu Trp 97 Thr Thr Thr Thr Thr 98 Phe Phe Phe Phe Phe 99 Gly Gly Gly Gly Gly F 100 Gly Gly Gly Gly Gly R 102 Thr Thr Thr Thr Thr 4 103 Lys Lys Lys Lys 1064 Leu Leu Leu Leu Leu 105 Glu Glu Glu Glu Glu 1106 Ile Ile Ile Leu Ile 11064			==	::		-:
96 Tyr Tyr Tyr Leu Trp 98 Phe Phe Phe Phe Phe 99 Gly Gly Gly Gly Gly F1000 Gly Gly Gly Gly Gly R100 Gly Gly Gly Gly Gly R100 Gly Gly Gly Gly R100 Lys Lys Lys Lys 1014 Leu Leu Leu Leu Leu 105 Glu Glu Glu Glu Glu 106 Ile Ile Ile Leu Ile 1060	950		,	رجـــ		
96 Tyr Tyr Tyr Leu Trp  97 Thr Thr Thr Thr Thr  98 Phe Phe Phe Phe Phe  99 Gly Gly Gly Gly Gly  F 100 Gly Gly Gly Gly Gly  R 102 Thr Thr Thr Thr  4 103 Lys Lys Lys Lys  106 Glu Glu Glu Glu  106 Ile Ile Ile Leu Ile  1064						
98 Phe 4Phe Phe Phe Phe 98 Gly	*					Trp
991 Gly Gly Gly Gly Gly Gly Fi 1007 Gly		The	<u>Ə Thr</u>	Thr	Thr	
R 100/ Gby Gly Gly, Ala Gly R 101/ Gly, Gly Gly Gly The The The The The The A 103 Lys Lys Lys Lys D104 Leu Leu Leu Leu, Leu Leu 1105 Glu	, .					
A 101 Gly Gly Gly Gly Gly Thr Thr Thr Thr Lys Lys Lys Lys Lys Lys Loud Leu			≎ Gly	Gly	Ala	
A:103 Lys Lys Lys Lys Lys 10104 Leu Dleu Dleu; Leu Leu 105 Glu Glu Glu Glu Glu 106 Ile Ile Leu Ile	p 7 101	Gly	Gly	∂Gly.	Gly	
70104 Leub Leu Deun Leu Leu 1105 Glu Glu Glu Glu Glu Glu 1106 Ile Ile Ile Leu Ile	4 102	3 .				_
106 Ile Ile Ile Leu Ile		Leu	∂ Leu	OLeu	Leu	
1064	··· 7 105°	Glu	~ Gl u	∵Gl u	, "Gla:	
1004 Lys Lys Lys Lys Lys					Leu	
	14107				•	
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# **EUROPEAN SEARCH REPORT**

EP 94 11 5683

ategory	Citation of document with of relevant p	indication, where appropriate,	Relevant 16	CLASSIFICATION OF THE APPLICATION (Int.CL6)
<b>A</b>	US-A-5 208 146 (R. * the whole docume	ERIE)	1-27	C12N15/13 C07K16/42
<b>\</b>	WO-A-89 00050 (AKZ * claims * * examples *	ing the second of the second o	1-27	
1	WO-A-93 10221 (THE UNIVERSITY OF CALI * the whole docume	FORNIA) & . 1	4-27 20 4	1
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# **EUROPEAN SEARCH REPORT**

Application Number 11 5683

CANCER RESEARCH, vol.52, no.9, 1 May 1992, PHILADELPHIA PA, USA pages 2603 - 2609' W. TADDEL-PETERS ET AL. 'Quantitation of human tumor-reactive monoclonal antibody 16.88 in the circulation and localization of 16.88 in colorectal metastatic tumor-3- tissue using murine antiidiotypic antibodies.' * abstract *  MOLECULAR IMMUNOLOGY, vol.30, no.16, November 1993, OXFORD, GB pages 1481 - 1489 K. YAGO ET AL. 'Immunoglobulin variable region sequences of two human-monoclonal antibodies directed to an onco-developmental carbohydrate antigen, lactotetraosylceramide (LcOse4Cer).'  * abstract **  TECHNICAL FIELDS SAACHED.  Files of search THE HAGUE  THE HAGUE  CATEGORY OF CITED DOCUMENTS  X: particularly relevant if taken alone Y: particularly relevant if taken alone	ategory		th indication, where appropriate, passages	Relevant to claim	CLASSIFICATION OF TO APPLICATION (Int.CL6)	HE
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